Updates in Hypertension and Cardiovascular Protection
Series Editors: Giuseppe Mancia · Enrico Agabiti Rosei

Michel Burnier *Editor*

Drug Adherence in Hypertension and Cardiovascular Protection

ESH European Society of Hypertension

Springer

Updates in Hypertension and Cardiovascular Protection

The aim of this series is to provide informative updates on both the knowledge and the clinical management of a disease that, if uncontrolled, can very seriously damage the human body and is still among the leading causes of death worldwide. Although hypertension is associated mainly with cardiovascular, endocrine, and renal disorders, it is highly relevant to a wide range of medical specialties and fields – from family medicine to physiology, genetics, and pharmacology. The topics addressed by volumes in the series *Updates in Hypertension and Cardiovascular Protection* have been selected for their broad significance and will be of interest to all who are involved with this disease, whether residents, fellows, practitioners, or researchers.

More information about this series at http://www.springer.com/series/15049

Michel Burnier
Editor

Drug Adherence in Hypertension and Cardiovascular Protection

European Society of Hypertension

Springer

Editor
Michel Burnier
Service of Nephrology and Hypertension
CHUV, University of Lausanne
Lausanne
Vaud
Switzerland

ISSN 2366-4606 ISSN 2366-4614 (electronic)
Updates in Hypertension and Cardiovascular Protection
ISBN 978-3-319-76592-1 ISBN 978-3-319-76593-8 (eBook)
https://doi.org/10.1007/978-3-319-76593-8

Library of Congress Control Number: 2018940263

Printed on acid-free paper

This Springer imprint is published by the registered company Springer International Publishing AG part of Springer Nature
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

When asked about the difficulties encountered in the management of patients with cardiovascular risk factors such as hypertension, dyslipidemia, and diabetes, most practicing physicians and healthcare providers will admit that adherence to recommendations and prescribed therapies is a critical issue. This is not very new as several centuries ago, Hippocrates was already warning physicians that "[they] should keep aware of the fact that patients often lie when they state that they have taken certain medicines."

In cardiovascular medicine, strong evidence has been gathered over the last 10 years indicating that adherence to drug therapy is a major determinant of success in the primary and secondary prevention of cardiovascular events. Nevertheless, drug adherence remains the "poor relation" of disease management in all therapeutic fields. Thus, there is still a surprising discrepancy between the recognized importance and relevance of the topic and the relatively low enthusiasm for the domain in clinical practice as well as in research.

Several factors contribute to this apparent discrepancy including a lack of knowledge, methodological limitations, limited time and resources to implement strategies supporting adherence, and a lack of cooperation within healthcare providers. However, in hypertension, the interest for drug adherence has increased suddenly with the recognition of the importance of non-adherence as a cause of resistant hypertension. Hence, within a few years, many new developments have become available that can now be used not only in reference centers or in clinical studies but also in clinical practice. These novelties take advantage of the new technologies such as digital medicine, biochemical analysis based on high-performance liquid chromatography-tandem mass spectrometry, information and mobile health technologies, and large national or regional prescription databases.

The goal of this book is to present these various new aspects of the adherence-related sciences. The book discusses the most recent data obtained with new technologies, but it will also cover other, more humanistic aspects, such as ethical aspects and interdisciplinary approaches involving nurses and pharmacists. Therefore, the book should catch the attention of healthcare students and professionals but also of industrial developers and specialists of e-technologies.

Improving adherence is a major challenge for healthcare systems, and in order to encourage everybody to join the effort, I would like to cite Hayden B. Bosworth from Duke University and the National Consumers League who claimed that "*…more health benefits worldwide would result from improving adherence to existing treatments than developing any new medical treatments*."

Lausanne, Switzerland Michel Burnier

Contents

Taxonomy of Medication Adherence: Recent Developments

1

Michel Burnier and Bernard Vrijens

1.1 Introduction

The observation that patients do not necessarily follow recommendations provided by their physicians or health care providers is probably as old as medicine and one may wonder whether a poor adherence to instructions is not an intrinsic property of human beings. Already several hundred years before Jesus Christ, Hippocrates was warning physicians that "*they should keep aware that patients often lie when they state that they have taken certain medicines.*" This statement remains valid more than 2000 years later.

Even though adherence to prescriptions is a very old issue, the modern area of adherence to drug therapy has started in the mid-1970s when the Mac Masters University Medical Center organized a scientific event focused on patient compliance. The major objective of this event was to discuss the potential clinical consequences of non-compliance and in particular the impact of non-compliance on the results of clinical trials. At that time, one concern was the ability to assess quantitatively the correspondence between what has been prescribed and what has really been implemented by the patients. These discussions lead to the publication of a seminal book on drug adherence entitled "Compliance with Therapeutic Regimens" by Sackett and Haynes [1]. Thereafter, several other key publications contributed to the recognition of drug adherence as a major problem in clinical medicine as well as in clinical research. Thus, in 1995, the Royal Pharmaceutical Society of Great

M. Burnier (✉)
Service of Nephrology and Hypertension, University Hospital, Lausanne, Switzerland
e-mail: michel.burnier@chuv.ch

B. Vrijens
University of Liège, Liège, Belgium

Advanced Analytical Research on Drug Exposure (AARDEX Group), Visé, Belgium
e-mail: bernard.vrijens@aardexgroup.com

M. Burnier (ed.), *Drug Adherence in Hypertension and Cardiovascular Protection*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-76593-8_1

Britain introduced the term of concordance, emphasizing the need for patients and health care providers to cooperate on the prescribed treatment [2, 3]. The Society also proposed a massive financial investment for research in the field. In 1997, the American Heart Association published its own statement and definition of adherence to therapy with a call for action addressed to health care professionals [4]. Once again the text points to the importance of involving patients in any choice and decision but also to the role of the patient's environment including the health care system.

In 2003, the World Health Organization (WHO) published a very important report on "Adherence to Long-term Therapies" focusing on all important clinical and economic consequences of a poor adherence and on the need to develop strategies to improve it [5]. In contrast to previous reports, the WHO recommendations were not limited to drug therapy and include all aspects of the patients' management such as diet or lifestyle changes. Therefore, they suggested a new definition according to which adherence is *"the extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider."*

In 2012, a new taxonomy has been published by Vrijens et al. as part of a FP7 European project entitled "Ascertaining Barriers for Compliance: policies for safe, effective and cost-effective use of medicines in Europe" (ABC project) [6]. This taxonomy will be discussed below in more details. Table 1.1 summarizes some of the most relevant definitions of adherence.

Table 1.1 More relevant definitions of adherence/compliance to medications over time

Source	Date	Definition
Sackett DL and Haynes RB [1]	1976	Compliance is the extent to which the **patient's** behavior (in terms of taking medications, following diets, or executing other lifestyle changes) coincides with the clinical prescription
Haynes RB	1979	Compliance is the extent to which a **person's** behavior (in terms of taking medication, following diets, or executing other lifestyle changes) coincides with medical or health advices
Dracup KA and Meleis AL [18]	1982	Compliance is the extent to which an individual chooses behaviors that coincide with a clinical prescription; the regimen must be consensual, that is, achieved through negotiations between the health professional and the patient
World Health Organization (WHO) [5]	2003	Adherence is the extent to which a person's behavior—taking medication, following a diet, and/or executing lifestyle changes—corresponds with agreed recommendations from a health care provider
Balkrishnan R [19]	2005	Adherence is the extent to which a patient participates in a treatment regimen after he or she agrees to that regimen
Cramer, J et al. [8]	2008	Medication compliance is the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen
ABC project (European consensus) [6]	2012	Adherence is the process by which patients take their medications as prescribed, composed of *initiation, implementation,* and *discontinuation*

1.2 Terminology: The Difficulty of Choosing the Right Term!

Since the 1970s, many terms have been used to characterize the difficulties that patients encounter in taking their treatments as prescribed. Thus, terms such as concordance, agreement, cooperation, therapeutic alliance, compliance, observance, adhesion, and finally adherence can be found in the literature. The variety of terms may be even greater depending on the subtleties of each language. Selecting the correct term has been relatively difficult not only because of the meaning of the word itself but also because of the conceptual meaning and the possible associations of ideas. Thus, in 1990, Feinstein commented on the proliferation of terms representing compliance, describing reasons why some synonyms were not superior to others: *"Adherence seems too sticky; Fidelity has too many connotations; and Maintenance suggests a repair crew. Although Adherence has its adherents, Compliance continues to be the most popular term"* [7]. Some of these terminologies have been progressively abandoned because they did not really represent the concept of partnership between patients, prescribers, and health care providers, and had a too strong connotation of obedience of the patient to the physicians' recommendations or prescriptions. Today, adherence appears to be the preferred term though compliance is still frequently used as a synonym [6, 8].

1.3 The New European Consensus-Based terminology

In 2009, at the Annual meeting of the European Society for Patients Adherence, Compliance, and Persistence (ESPACOMP), a first consensus meeting was organized to define a new terminology/taxonomy describing patient's medicines-taking behavior. Eighty persons from 13 countries attended this meeting and participated to the discussion. Interestingly, they were of different professional horizons but all were in one way or another linked to patients' care with medications. The first consensus document was then submitted for discussion in several following meetings until a final publication was released in 2012 [6]. The panel concluded that a difference should be made between the ***processes*** such as adherence to medications and the management of adherence, and the ***discipline*** studying these processes, i.e., the adherence-related sciences.

In this new taxonomy, *adherence to medications* is defined as the process by which patients take their medications as prescribed. Three components are parts of this process: the *initiation*, the *implementation*, and the *discontinuation.* As illustrated in Fig. 1.1, drug therapy starts with the initiation, i.e., when the patient takes the first dose of the prescribed medication. It is a yes or no phenomenon. Thereafter, the implementation is the extent to which the patient's actual dosing is in accordance with the prescribed dosing regimen between the initiation and the last dose. It is measured over a period of time and generally reported as a percentage. At last, discontinuation occurs when the patient stops taking the prescribed medication

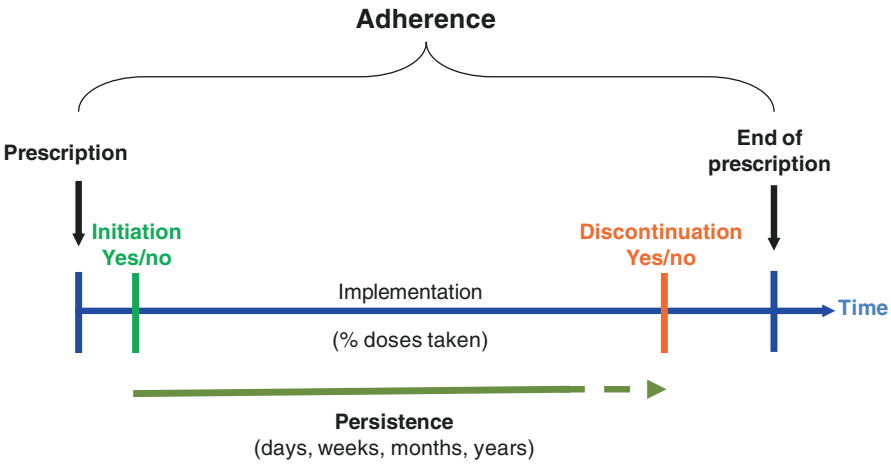


Fig. 1.1 The new taxonomy of adherence to medications according to the ABC European Consensus project

for whatever reason. The discontinuation can be initiated by the patient or by the clinician.

Clinically, the most important measure of drug utilization in chronic diseases is certainly ***persistence*** which represents the time between initiation and the last dose before sustained discontinuation. It is a time to event variable, which can be measured and reported as a continuous variable in terms of number of days for which therapy is available and medication is taken, more or less consistently (Fig. 1.1). Sometimes, persistence is also reported as a dichotomous variable patients being "persistent" or "non-persistent" based on a predefined cutoff and duration of monitoring. In chronic diseases such as hypertension and dyslipidemia, a lack of persistence is an important problem limiting the benefits of primary or secondary cardiovascular prevention [9]. According to these different parameters, several clinical profiles of poor or non-adherence to drug therapy can possibly be observed in clinical practice.

1.4 Terminologies Associated with the Quantification of Adherence to Medications

One of the major difficulties in the *Management of Adherence* aiming at improving and supporting patients' adherence to medications is to obtain a reliable quantification of the adherence process over time. Indeed, as a general rule, no process can be improved if it cannot be measured adequately. The development of new approaches to measure and quantify more precisely drug adherence has actually been one of the main target of adherence-related sciences during the last decades. Although several approaches to assess adherence to medications are now available, as will be discussed in following chapters (see chapters 3, 4, 6 and 7), very few of them provide

a dosing history that helps tackling the many day-to-day barriers that patients are encountering during their treatments.

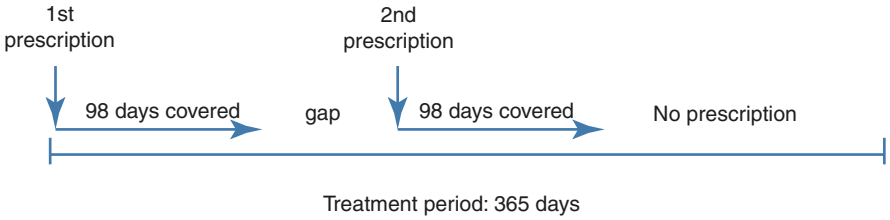
When a dosing history is available, several quantification variables can be calculated and evaluated statistically. To this purpose, these parameters also need to be defined properly.

Among those one may cite the following:

(a) The proportion of prescribed drug taken
(b) The proportion of days with the correct number of doses taken (so-called "*taking adherence*")
(c) The proportion of doses taken on time ("*timing adherence*") respecting the dosing intervals
(d) The number of drug holidays defined as intervals of time (days, weeks, …) when a patient temporarily stops taking the medication
(e) The distribution and duration of intervals between two doses

These qualitative and quantitative assessments of adherence based on a dosing history provide the best information on patients' behaviors which should be used in clinical practice to develop individual solutions to improve long-term adherence and persistence.

In the last 30 years, computerized administrative health databases have become more and more common. A variety of databases exists ranging from those containing only pharmacy data to data sets incorporating electronic medical records with comprehensive claims information including clinical data and diagnosis information. Today, these datasets are increasingly used to assess drug prescription and utilization patterns as well as drug persistence in large groups of patients or in populations using for example case-control studies. They have now become a new source of medical evidence [10, 11]. Unfortunately, most of the time, these databases do not provide any dosing history but rather data on medication prescriptions and refills during a defined period enabling essentially an assessment of persistence. These approaches will be discussed in detail in following chapters (see chapters 5 and 13). One of the main advantages of recent health care databases or registries is that persistence data can be coupled to the associated impact on patients' health and health-system use [12–14]. The main variable of the analyses performed on these registries is the calculation of the **medication possession ratio (MPR)** defined as the ratio of total days of medication supplied (not including the last prescription) to total days in a period of time. Thus, persistence can be quantified calculating the cumulative number of days in which the medication is available divided by the days of the overall follow-up, the ratio expressing the ***proportion of days covered*** (PDC) by the treatment [15]. The difference between PDC and MPR is that with PDC any oversupply is truncated, whereas values of greater than 100% are allowed with the MPR (Fig. 1.2). Thereafter, persistence can eventually be categorized such as a very low (≤25%), a low (26–50%), an intermediate (51–75%), and a high (>75%) PDC value. In some cases, patients are considered as non-persistent if they have a gap of more than 30 or 60 days between end of dispensed supply and next dispensed



Medication possession ratio (MPR):

number of days covered 2 x 98 = 196 days
observation time: 365 days

MPR = 196/365 = 53%

In this case, the MPR is equivalent to the percentage of days covered (see text)

Fig. 1.2 Illustration of the calculation of the medication possession ratio

prescription. In many publications, an arbitrary threshold is defined to distinguish "adherent" from "non-adherent" patients. This threshold is often set at 80%. However, one has to acknowledge that this percentage is not supported by specific researches validating the appropriateness of this cutoff for given drug classes or diseases. In some clinical circumstances, lower or higher cutoffs may be more accurate depending on the characteristics of the disease and the pharmacological profile of drugs.

In a recent publication [16], Raebel et al. have proposed some new terminologies and definitions of medication adherence and persistence in research employing electronic databases. Reviewing the literature, they suggested several definitions that are in line with previously published ones, replacing the term "initiation" by "primary adherence." However, they also define a newer metric named New Prescription Medication Gap (NPMG) measure [17]. This measure is defined as the proportion of days within an interval bounded by the prescriber's initial electronic health record prescription medication order date and the end of the observation period (or end of follow-up if censored or the therapy is switched or discontinued). Therefore, in contrast to the MPR, this metric starts with the date of prescription and includes the time until initiation. NPMG is a continuous measure, ranging from 100% for patients who obtain no medication to 0% for those who consistently refill their medication in a timely fashion [17].

Conclusions

In all domains of science, the availability of a precise terminology and clear definitions of major processes is absolutely necessary in order to avoid confusion and misunderstandings for example in scientific publications or comparative studies. This has been true for adherence-related sciences for many years as several terminologies and definitions with different meanings were used to describe the same processes and behaviors within the adherence to medication

framework. The work performed during the last years by the members of the ABC project team is of utmost value as it enables scientists and clinicians to use the same taxonomy but also the same metrics for quantitative assessments of parameters of adherence to medication. This more consistent taxonomy should as the authors concluded "*aid in the conduct, analysis, and interpretation of scientific studies of medication adherence*" (http:// www.ABCproject.eu). Its adoption could also help standardizing the medical literature and facilitate health politicians in their decisions regarding improvement of medication adherence.

References

1. Sackett DL, Haynes RB. Compliance with therapeutic regimens. Baltimore, MD: Johns Hopkins University Press; 1976.
2. Royal Pharmaceutical Society of Great Britain. From compliance to concordance: towards shared goals in medicine taking. London: Royal Pharmaceutical Society; 1997.
3. Mullen PD. Compliance becomes concordance. BMJ. 1997;314:691–2.
4. Miller NH, Hill M, Kottke T, Ockene IS. The multilevel compliance challenge: recommendations for a call to action. A statement for healthcare professionals. Circulation. 1997;95:1085–90.
5. World Health Organization. Adherence to long term therapies: evidence for action. Geneva: World Health Organization; 2003.
6. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, Dobbels F, Fargher E, Morrison V, Lewek P, Matyjaszczyk M, Mshelia C, Clyne W, Aronson JK, Urquhart J, ABC Project Team. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol. 2012;73:691–705.
7. Feinstein AR. On white-coat effects and the electronic monitoring of compliance. Arch Intern Med. 1990;150:1377–8.
8. Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, Wong PK. Medication compliance and persistence: terminology and definitions. Value Health. 2008;11:44–7.
9. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. Am J Med. 2012;125:882–7.e1.
10. Corrao G, Mancia G. Generating evidence from computerized healthcare utilization databases. Hypertension. 2015;65:490–8.
11. Hasselstrom J, Zarrinkoub R, Holmquist C, Hjerpe P, Ljungman C, Qvarnstrom M, Wettermark B, Manhem K, Kahan T, Bengtsson Bostrom K. The Swedish Primary Care Cardiovascular Database (SPCCD): 74 751 hypertensive primary care patients. Blood Press. 2014;23:116–25.
12. Corrao G, Rea F, Ghirardi A, Soranna D, Merlino L, Mancia G. Adherence with antihypertensive drug therapy and the risk of heart failure in clinical practice. Hypertension. 2015;66:742–9.
13. Mazzaglia G, Mantovani LG, Sturkenboom MC, Filippi A, Trifiro G, Cricelli C, Brignoli O, Caputi AP. Patterns of persistence with antihypertensive medications in newly diagnosed hypertensive patients in Italy: a retrospective cohort study in primary care. J Hypertens. 2005;23:2093–100.
14. Qvarnstrom M, Kahan T, Kieler H, Brandt L, Hasselstrom J, Bengtsson Bostrom K, Manhem K, Hjerpe P, Wettermark B. Persistence to antihypertensive drug treatment in Swedish primary healthcare. Eur J Clin Pharmacol. 2013;69:1955–64.
15. Halpern MT, Khan ZM, Schmier JK, Burnier M, Caro JJ, Cramer J, Daley WL, Gurwitz J, Hollenberg NK. Recommendations for evaluating compliance and persistence with hypertension therapy using retrospective data. Hypertension. 2006;47:1039–48.

16. Raebel MA, Schmittdiel J, Karter AJ, Konieczny JL, Steiner JF. Standardizing terminology and definitions of medication adherence and persistence in research employing electronic databases. Med Care. 2013;51:S11–21.
17. Karter AJ, Parker MM, Moffet HH, Ahmed AT, Schmittdiel JA, Selby JV. New prescription medication gaps: a comprehensive measure of adherence to new prescriptions. Health Serv Res. 2009;44:1640–61.
18. Dracup KA, Meleis AI. Compliance: an interactionist approach. Nurs Res. 1982;31:31–6.
19. Balkrishnan R. The importance of medication adherence in improving chronic-disease related outcomes: what we know and what we need to further know. Med Care. 2005;43:517–20.

Part I

Measuring Drug Adherence

Qualitative Assessments of Adherence

2

Michel Burnier and Grégoire Wuerzner

2.1 Introduction

When asked about the major issues in the management of chronic diseases such as hypertension, almost all healthcare providers will cite adherence or compliance to medications and recommendations. Indeed, a poor adherence to therapy has long been recognized as a significant health problem leading to high healthcare costs and poor patients' outcomes in all fields of clinical medicine [1–3]. However, when asked about their approach to assess adherence in clinical practice, the same professionals—physicians, nurses, and pharmacists—admit that they are very limited in their ability to diagnose accurately a problem of adherence not only because of a lack of time but mainly because they do not have the adequate tools and they do not feel confident in their own competences to identify non-adherence [4].

There are multiple reasons why physicians, nurses, or pharmacists may feel uncomfortable with the recognition of problems of adherence to medications. First, the process of adherence is extremely variable and may occur anytime during the medication-taking process. Indeed, adherence to therapy is a **dynamic process** and a patient may decide to withhold or interrupt his/her treatment for many good or bad reasons either very soon, at the initiation, because of beliefs or acute side effects, or after several weeks or months during the implementation, because of long-term side effects, forgetfulness, carelessness, or personal or socioeconomic contrarieties. Thus, healthcare professionals should be almost constantly in alert of a poor adherence issue that may interfere with the control of clinical parameters, for example blood pressure. The second reason is that physicians have only limited tools to perform a reliable diagnosis of poor adherence to medications in their office. Indeed, for many

M. Burnier (✉) G. Wuerzner
Department of Medicine, Service of Nephrology and Hypertension, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland
e-mail: michel.burnier@chuv.ch; gregoire.wuerzner@chuv.ch

M. Burnier (ed.), *Drug Adherence in Hypertension and Cardiovascular Protection*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-76593-8_2

years the majority of diagnostic tools have been developed in the context of clinical research but not for a daily use in a clinical setting. Thus many of them are either too time-consuming or complex or expensive to be conducted outside a study. At last, although several methods are available, accurate measurements are still few and there is no generally accepted "gold standard" to assess adherence [5, 6].

In practice, there are numerous reasons and ways to measure adherence. Among the different purposes, methods have been established essentially to monitor the medication-taking behavior but also to assess the beliefs and the barriers associated with adherence [7]. Questionnaires have also been developed to assess other aspects of the management of cardiovascular diseases such as adherence to lifestyle changes or dietary recommendations. Regarding the methods of measurement, qualitative and quantitative approaches can be used. Objective measures such as pill count, electronic monitoring, use of pharmacy records, direct observed therapy, and determinations of drug concentrations will be discussed in the following chapters of this book. This chapter will focus on qualitative measures such as patient's interviews, patients' self-report, and scaled questionnaires.

2.2 What Are the Characteristics of a Valid and Useful Method to Assess Adherence to the Medication?

Whether it is objective or subjective, the ideal method to measure adherence to the medication in clinical practice should be cheap, easy to carry out (feasible by different health professionals), user friendly, reliable with a good predictive value and before all validated in different clinical conditions. In addition, patients should not have the possibility to bias the answers according to their secret wishes. In 2015, Stirrat et al. have published a set of recommendations to improve the validity of self-reports measures of adherence [8]. They also provide some clues on how to develop valid self-reports of adherence. Table 2.1 shows one example of a set of recommendations to ameliorate self-reports in the future. Interestingly, they favor the use of computers rather than face-to-face data collection to reduce social desirability concerns and improve data quality [8].

Table 2.1 Ten ways of improving the validity of self-report measures

1.	Do not reinvent the wheel; choose a self-report adherence measure with validation data for your target population whenever possible
2.	Define the adherence construct of interest (i.e., extent of adherence vs. reasons for non-adherence) and select a measure containing items matched to that need
3.	Administer adherence measures **through computer surveys** rather than face-to-face data collection to reduce social desirability concerns and improve data quality
4.	In research contexts, staff members who collect adherence data should be separate from staff members who deliver adherence support or adherence interventions
5.	Introduce the self-report adherence measure with a statement which normalizes non-adherence to help address social desirability concerns

Table 2.1 (continued)

6.	Use a question response format that asks respondents to estimate their overall adherence behavior. Response items that characterize adherence in ordinal terms or quantitative continua (e.g., estimated percent of doses taken) may help reduce ceiling effects
7.	Use a self-report adherence measure that specifies a recall period for adherence behavior. A recall period of **the last 30 days** may reduce ceiling effects relative to shorter intervals
8.	Consider dichotomization of self-report adherence measures at the 100% mark to recognize their tendency for over-reporting relative to other adherence measures
9.	Add a social **desirability measure** to complement analysis of self-report adherence data
10.	Research publications should include clear descriptions of any self-report adherence measure, its administration method, and descriptive data resulting from the measure to help further the science

Adapted from reference [8]

2.3 The Patient Interviews by Physicians or Third Parties and Patient's Diaries

In general, the first step that physicians use when they are suspicious of non-adherence is to ask patients how they are managing their medications in their daily life and how often they are forgetting them. Indeed, patients should be the most reliable source of information provided they are willing to accept answering questions and admitting occasional phases of non-adherence. Interviewing the patient is definitively the easiest and cheapest approach to assess adherence in a clinical setting. However, in reality, it appears that interviewing patients provides little relevant information as to whether they are adherent or not and studies have consistently shown that interviews overestimate patients' adherence [5, 9]. Physicians tend to think that they obtain more pertinent information with the interview than any other approaches because they know their patients. Although it has been reported that patients with a good relationship with their physician have indeed a better adherence to therapy [10], the fact that physicians are following their patients for many years and know their patients' cultural beliefs and environment, is in no way a sufficient guarantee that they will obtain valid information on adherence. Indeed, the quality of the information will also depend on the communication skills of physicians and on their ability to create an encouraging and "blame-free" environment in which patients feel confident to honestly answer any questions related to their treatment [11]. One drawback of interviews is that patients tend to underreport periods of non-adherence, either involuntarily or on purpose, in order to please healthcare providers and/or avoid time-consuming and embarrassing discussions. This is also true for patient-kept diaries which tend to overestimate drug intake by about 30% when compared to an electronic monitoring [12]. This problem may be more pronounced in elderly patients with cognitive troubles [12]. Thus, as proposed by E.C Wright, physicians should not accept everything the patient is saying [13]. As an example, he cites the experience published by Davis TME et al. in which, using an anonymous multiple choice questionnaire, almost all of 100 patients with diabetes considered their fellow diabetics to be dishonest during outpatient consultations,

Table 2.2 Example of questions, physicians can ask to assess a patient's adherence to medications

1.	I know it must be difficult to take all your medications regularly. How often do you miss taking them?
2.	Of the medications prescribed to you, which ones are you taking?
3.	Of the medications you listed, which ones are you taking every day?
4.	Of the medications you listed, which ones did you forget this week?
5.	Have you had to stop any of your medication for any reason recently?
6.	How often do you not take medication X?
7.	When was the last time you took medication X?
8.	Have you noticed any adverse effects from your medications?

Adapted from reference [11]

and only 25% thought that the doctors believed everything they were told [14]. In the end, only patients who openly admit that they did not take their medications, can be trusted.

As mentioned by Wright EC: *"It is better to avoid the problem of poor compliance than to face its consequences"* [13]. Avoiding open discussions on lack of adherence is probably what most physicians do. One important issue is certainly their low ability to obtain reliable information on adherence to medication due to an absence of specific training on the way to ask direct questions in a nonjudgmental way [11]. Table 2.2 shows examples of questions that can be asked by physicians in order to encourage patients to give useful answers [11]. In a large study conducted in three Eastern European countries (Austria, Hungary, and Slovakia), interviews were performed by trained nurses and physicians using a very simple set of questions in more than 2800 subjects of whom 841 were hypertensive [15]. The results of this survey were that adherence to therapy based on simple questions about antihypertensive therapy and the frequency of missed doses correlated well with blood pressure control suggesting that in some conditions structured interviews might be useful.

Taken together, although it is generally agreed that patients' interviews are of limited reliability, reason why this method is never used in medical research, there is a clear potential for improvement. To this purpose specific training in how to interview a patient on adherence should be part of the curriculum of young physicians.

2.4 Use of Questionnaires in Hypertension

Questionnaires addressing various issues associated with adherence to the medication belong to qualitative and subjective assessments of adherence. They were initially developed to improve and to structure self-reports provided by the patients and the patients' interviews. In general, these questionnaires are filled in by the patients' themselves or with the help of healthcare professionals. In order to be clinically useful, they should be short, easy to administer, reliable, valid, reproducible, and internally coherent [16]. Most of them are used in clinical research and some others in clinical practice.

In a large systematic review of questionnaires and self-report adherence scales, Nguyen et al. identified 43 English written scales [7] but many others exist in different languages. These scales were categorized into five groups based on the nature of information gathered: the first group was seeking information on medication-taking behavior only, the second on medication-taking and barriers to adherence, the third on barriers to adherence only, the fourth was seeking information on beliefs, and the fifth group included questionnaires seeking information on barriers and beliefs. The majority of questionnaires (30/43) were focusing on medication-taking behavior assessing the number of doses taken or missed. One frequent limitation of these questionnaires was the absence of a precise definition of the time frame for the questions, this latter ranging from 1 day to 12 months.

It is behind the scope of this chapter to review all the self-report scales and questionnaires presented in Nguyen's review. However, we shall focus on the main questionnaires used essentially in the field of hypertension and cardiovascular diseases. In group 1 and 2 seeking specifically information on medication-taking behavior and barriers, following questionnaires can be considered: the Morisky–Green–Levine [17], the Adherence Self-Report Questionnaire [18], the Stages of Change for Adherence Measure [19], the Brief Medication Questionnaire [20], the Hill–Bone Compliance to High Blood Pressure Scale [21], and the Morisky Medication Adherence Scale (4 or 8 questions) [22]. These questionnaires in hypertension have been reviewed for their validity and reliability by B. Perez-Escamilla [16] and details on these questionnaires can be found in the review by Culig et al. [23].

The most well-known and probably used questionnaire is undoubtedly the Medication Adherence Questionnaire developed by Morisky et al. [17, 22]. In 1986 already, the four items questionnaire was evaluated in hypertensive patients. In this first assessment, the scale demonstrated both concurrent and predictive validity with regard to blood pressure control at 2 years and 5 years, respectively [17]. It is short (4 or 8 items) and enables to identify the medication-taking behavior, forgetfulness, and some barriers to non-adherence but not the patient's self-efficacy (Table 2.3). The internal consistency ranges between 0.56 and 0.83 (mean Cronbach α: 0.61) depending on the studies. The sensitivity ranged between 0.73 and 0.93 and the specificity between 0.36 and 0.53 [7]. It was compared to clinical outcome and to

Table 2.3 The Morisky 8 items questionnaire

1.	Do you sometimes forget to take your high blood pressure pills?
2.	Over the past 2 weeks, were there any days when you did not take your high blood pressure medicine?
3.	Have you ever cut back or stopped taking your medication without telling your doctor because you felt worse when you took it?
4.	When you travel or leave home, do you sometimes forget to bring along your medications?
5.	Did you take your blood pressure medicine yesterday?
6.	When you feel like your blood pressure is under control, do you sometimes stop taking your medicine?
7.	Taking medication everyday is a real inconvenience for some people. Do you ever feel hassled about sticking to your blood pressure treatment plan?
8.	How often do you have difficulty remembering to take all your blood pressure medication?

From reference [22]

Table 2.4 The Hill–Bone questionnaire

1.	How often do you forget to take your HBP medicine?
2.	How often do you decide not to take your HBP medicine?
3.	How often do you eat salty food?
4.	How often do you shake salt, fondor, aromat on your food before you eat it?
5.	How often do you eat fast food?
6.	How often do you get the next appointment before you leave the clinic?
7.	How often do you miss scheduled appointments?
8.	How often do you leave the dispensary without obtaining your prescribed pills?
9.	How often do you run out HBP pills?
10.	How often do you skip your HBP medicine 1–3 days before you go to the clinic?
11.	How often do you miss taking your HBP pills when you feel better?
12.	How often do you miss taking your HBP pills when you feel sick?
13.	How often do you take someone else's HBP pills?
14.	How often do you miss taking your HBP pills when you care less?

HBP high blood pressure
Answers range between: (1) none of the time, (2) some of the time, (3) most of the time, (4) all the time; *NA* not applicable, *DK* don't know
From reference [21]

pharmacy records. When compared to the medication events monitoring system (MEMS) which provides a complete dosing history, it appears that the Morisky questionnaire, like many other self-report scales, overestimates adherence to medication with a correlation of 0.26 between MEMS and self-report questionnaires in hypertensive patients [24]. Yet, some better correlations have been reported in other contexts [25]. Today the Morisky questionnaire has been translated and validated in many languages around the world.

The Hill–Bone Compliance to High Blood Pressure Scale has been specifically developed with a focus on hypertensive patients followed in general practice in South Africa [26]. It assesses the medication-taking behavior but also the adherence to dietary salt intake and to appointments. In this respect, this questionnaire cannot be used for other clinical conditions. As shown in Table 2.4, it consists of 14 items but was used sometimes with only 10 items. In a first study in 98 hypertensive patients, appointment-making and dietary salt-intake subscales were not internally consistent but regarding blood pressure control, a significant predictive validity was found in that noncompliance predicted higher diastolic blood pressures ($p = 0.21$, $P < 0.05$) and medication noncompliance tended to predict higher systolic blood pressures ($p = 0.20$, $P < 0.06$). In African and African-American it was found to have internal consistency with a Cronbach α of 0.74–0.84. It was compared to the Morisky questionnaire in a larger study including 353 hypertensive patients [27]. In this study, the ability to identify medication adherence was inconsistent for nearly

every third patient with both questionnaires. Therefore they did not recommend either questionnaire for clinical use. An adapted Turkish version was found to be more reliable [28].

The Brief Medication Questionnaire (BMQ) focuses essentially on the drug regimen and to some extent on barriers to adherence [20]. The BMQ asks patients to reconstruct their medication regimens over the preceding week, including the names of the medications, dosages, indications, and self-report of missed doses. It was found to have a sensitivity of 80% and specificity of 1.0. It was developed based on a literature review and patient feedback. It was compared to the MEMS system in a small group of 20 patients and a good correlation was found.

The Adherence Self-Report questionnaire (ASRQ) is based on six descriptions corresponding to six levels of adherence. It was tested in 245 patients with uncontrolled hypertension taking part in a randomized study. The data provided by the questionnaire were compared to the MEMS data over a period of 30 days in 66 patients [18]. In this study, a decrease of one adherence level was associated with a decrease in timing compliance. Using the cutoff of those who reported ASRQ levels 1 and 2 (all tablets taken but not always at the same time of day), a high percentage of those with comparatively high adherence according to MEMS were correctly identified (specificity, 90–93%; negative predictive value, 66–96%). However, sensitivity (detection of true non-adherent patients) and positive predictive values were poor to moderate (14–42% and 22–66%, respectively) [29]. The correlation between the MEMS and the ASRQ was 0.29 [25]. Some other adherence scales were developed in recent years in different countries. Thus, Culig et al. designed a self-administered questionnaire listing 16 common reasons for non-adherence [23]. The internal consistency reliability of this questionnaire was found to be a α value of 0.89. It was tested in pharmacies in 635 patients with chronic diseases including 361 patients with hypertension.

Conclusions

Tracking down non-adherence in clinical practice is a very difficult task for healthcare professionals. The performance of the numerous self-report questionnaires or scales is rather limited and this is not really surprising if one considers the high variability and dynamic of adherence to medication in patients with chronic diseases. In most circumstances, questionnaires can be considered as complements to more objective measures mainly because these latter ones are either expensive or not convenient to be repeated so frequently. Nonetheless, when compared to drug measurements in plasma or urine or electronic measurements of adherence, questionnaires may provide additional information, for example on the reasons why patients do not adhere to their prescribed therapy or on the barriers to which patients are confronted during their medication-taking process. Self-report questionnaires may also inform physicians on the patients' beliefs. If healthcare providers take sufficient time to listen to these important aspects of adherence to medications, qualitative assessments of adherence will remain useful complementary tools to tackle poor adherence not only in clinical studies but also in clinical practice.

References

1. Sabaté E. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization; 2003.
2. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. Med Care. 2005;43:521–30.
3. Corrao G, Parodi A, Nicotra F, Zambon A, Merlino L, Cesana G, Mancia G. Better compliance to antihypertensive medications reduces cardiovascular risk. J Hypertens. 2011;29:610–8.
4. Hill MN, Miller NH, DeGeest S, American Society of Hypertension Writing Group. ASH position paper: Adherence and persistence with taking medication to control high blood pressure. J Clin Hypertens (Greenwich). 2010;12:757–64.
5. Vik SA, Maxwell CJ, Hogan DB. Measurement, correlates, and health outcomes of medication adherence among seniors. Ann Pharmacother. 2004;38:303–12.
6. Krousel-Wood M, Thomas S, Muntner P, Morisky D. Medication adherence: a key factor in achieving blood pressure control and good clinical outcomes in hypertensive patients. Curr Opin Cardiol. 2004;19:357–62.
7. Nguyen TM, La Caze A, Cottrell N. What are validated self-report adherence scales really measuring?: a systematic review. Br J Clin Pharmacol. 2014;77:427–45.
8. Stirratt MJ, Dunbar-Jacob J, Crane HM, Simoni JM, Czajkowski S, Hilliard ME, Aikens JE, Hunter CM, Velligan DI, Huntley K, Ogedegbe G, Rand CS, Schron E, Nilsen WJ. Self-report measures of medication adherence behavior: recommendations on optimal use. Transl Behav Med. 2015;5:470–82.
9. Zeller A, Taegtmeyer A, Martina B, Battegay E, Tschudi P. Physicians' ability to predict patients' adherence to antihypertensive medication in primary care. Hypertens Res. 2008;31:1765–71.
10. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353:487–97.
11. Brown MT, Bussell JK. Medication adherence: WHO cares? Mayo Clin Proc. 2011;86:304–14.
12. Straka RJ, Fish JT, Benson SR, Suh JT. Patient self-reporting of compliance does not correspond with electronic monitoring: an evaluation using isosorbide dinitrate as a model drug. Pharmacotherapy. 1997;17:126–32.
13. Wright EC. Non-compliance—or how many aunts has Matilda? Lancet. 1993;342:909–13.
14. Davis TME, Strong J, Bloom SR. Compliance in diabetes mellitus: a self-assessment study. Pract Diabetes. 1988;5:170–2.
15. Fodor GJ, Kotrec M, Bacskai K, Dorner T, Lietava J, Sonkodi S, Rieder A, Turton P. Is interview a reliable method to verify the compliance with antihypertensive therapy? An international central-European study. J Hypertens. 2005;23(6):1261.
16. Perez-Escamilla B, Franco-Trigo L, Moullin JC, Martinez-Martinez F, Garcia-Corpas JP. Identification of validated questionnaires to measure adherence to pharmacological antihypertensive treatments. Patient Prefer Adherence. 2015;9:569–78.
17. Morisky DE, Green LW, Levine DM. Concurrent and predictive validity of a self-reported measure of medication adherence. Med Care. 1986;24:67–74.
18. Schroeder K, Fahey T, Hay AD, Montgomery A, Peters TJ. Adherence to antihypertensive medication assessed by self-report was associated with electronic monitoring compliance. J Clin Epidemiol. 2006;59:650–1.
19. Willey C, Redding C, Stafford J, Garfield F, Geletko S, Flanigan T, Melbourne K, Mitty J, Caro JJ. Stages of change for adherence with medication regimens for chronic disease: development and validation of a measure. Clin Ther. 2000;22:858–71.
20. Svarstad BL, Chewning BA, Sleath BL, Claesson C. The Brief Medication Questionnaire: a tool for screening patient adherence and barriers to adherence. Patient Educ Couns. 1999;37:113–24.
21. Kim MT, Hill MN, Bone LR, Levine DM. Development and testing of the hill-bone compliance to high blood pressure therapy scale. Prog Cardiovasc Nurs. 2000;15:90–6.

22. Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. J Clin Hypertens (Greenwich). 2008;10:348–54.
23. Culig J, Leppee M. From Morisky to Hill-bone; self-reports scales for measuring adherence to medication. Coll Antropol. 2014;38:55–62.
24. Hamilton GA. Measuring adherence in a hypertension clinical trial. Eur J Cardiovasc Nurs. 2003;2:219–28.
25. Shi L, Liu J, Fonseca V, Walker P, Kalsekar A, Pawaskar M. Correlation between adherence rates measured by MEMS and self-reported questionnaires: a meta-analysis. Health Qual Life Outcomes. 2010;8:99.
26. Lambert EV, Steyn K, Stender S, Everage N, Fourie JM, Hill M. Cross-cultural validation of the hill-bone compliance to high blood pressure therapy scale in a South African, primary healthcare setting. Ethn Dis. 2006;16:286–91.
27. Koschack J, Marx G, Schnakenberg J, Kochen MM, Himmel W. Comparison of two self-rating instruments for medication adherence assessment in hypertension revealed insufficient psychometric properties. J Clin Epidemiol. 2010;63:299–306.
28. Karademir M, Koseoglu IH, Vatansever K, Van Den Akker M. Validity and reliability of the Turkish version of the Hill-Bone compliance to high blood pressure therapy scale for use in primary health care settings. Eur J Gen Pract. 2009;15:207–11.
29. Zeller A, Schroeder K, Peters TJ. An adherence self-report questionnaire facilitated the differentiation between nonadherence and nonresponse to antihypertensive treatment. J Clin Epidemiol. 2008;61:282–8.

3 Electronic Monitoring of Medication Adherence: From Dose-Counting to Dose-Clocking

Bernard Vrijens and Eric Tousset

3.1 History of MEMS Monitoring and Bibliometry

The first electronic monitor for medication adherence, known as the Medication Event Monitoring System (MEMS®), was initially tested in 1977. The MEMS principle consists in the incorporation of a microcircuitry into pharmaceutical packages of various designs such that the manoeuvers needed to remove a dose of drug were detected in real time, time stamped, analyzed, stored, and communicated. MEMS was originally designed as an electronic cap to capture the opening and closing of a standard pharmaceutical bottle (see Fig. 3.1). The principle can easily be extended to blister packaging, injectable, inhaler, or other types of drug deliveries.

To date, over 750 papers, published in peer-reviewed journals, report diverse uses of MEMS® involving more than one million trial subjects. Those papers have been cited over 65,000 times, and, collectively, have a h-index of 132, which, among other things, means that a paper describing clinical research findings with MEMS monitoring has a 1 in about 5 chance to end up with >132 citations. The most cited MEMS paper is by Paterson et al. [1], *with more than 3300 citations.* This seminal paper brought to light a major surprise with the finding that life-threatening diseases do not, ipso facto, enforce strict implementation of prescribed regimen(s). This fact

B. Vrijens (✉)
Advanced Analytical Research on Drug EXposure (AARDEX Group), Visé, Belgium

Department of Public Health, University of Liège, Liège, Belgium
e-mail: bernard.vrijens@aardexgroup.com

E. Tousset
Advanced Analytical Research on Drug EXposure (AARDEX Group), Visé, Belgium
e-mail: eric.tousset@aardexgroup.com

M. Burnier (ed.), *Drug Adherence in Hypertension and Cardiovascular Protection*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-76593-8_3

Fig. 3.1 Evolution of the MEMS® Cap from version 1 in 1977 to version 8 in 2017

became evident not only in the fields of HIV-AIDS, but also in organ transplantation [2], and more recently in cancer chemotherapy [3].

In ambulatory care, across most therapeutic areas, electronic monitoring of patients' dosing histories has repeatedly revealed that the drug intake of patients is frequently irregular, spanning a wide spectrum of deviations from the prescribed regimen. It is strongly skewed toward under-dosing, created by delayed and omitted doses, sometimes resulting in multiple, sequential omissions of prescribed doses. The consequences of nonadherence include (*a*) failed treatment; (*b*) inappropriate dose escalation; (*c*) emergence of drug-resistance to infectious microorganisms such as tuberculosis and human immunodeficiency virus (HIV); (*d*) hazardous rebound or recurrent first-dose effects; and (*e*) misdiagnosis, when drug response is a diagnostic criterion. Partial adherence or nonadherence can also be a confounding factor in the interpretation of clinical trial results, with consequences that include underestimated efficacy of new drugs, to the point of trial failure; underestimated incidence of adverse effects; distorted pharmaco-economic analyses; and/or overestimated dosing requirements for marketed pharmaceuticals [4].

3.2 Indirect Versus Direct Measure

Electronic detection of package entry is an indirect measure of dose intake and there could be instances where the package is activated but a dose is not taken. Studies [5] comparing MEMS cap data with drug concentrations show that there is 97% accuracy between opening the pharmaceutical package and time of ingestion of the prescribed dose. This evidence advocates that MEMS packaging provides a very accurate measure of adherence and, even more importantly, insightful information

of each individual's drug-taking behaviors. The value of MEMS information to distinguish between the different adherence behaviors is illustrated in Fig. 3.2. Those dosing chronology plots spot different intake patterns and highlight the

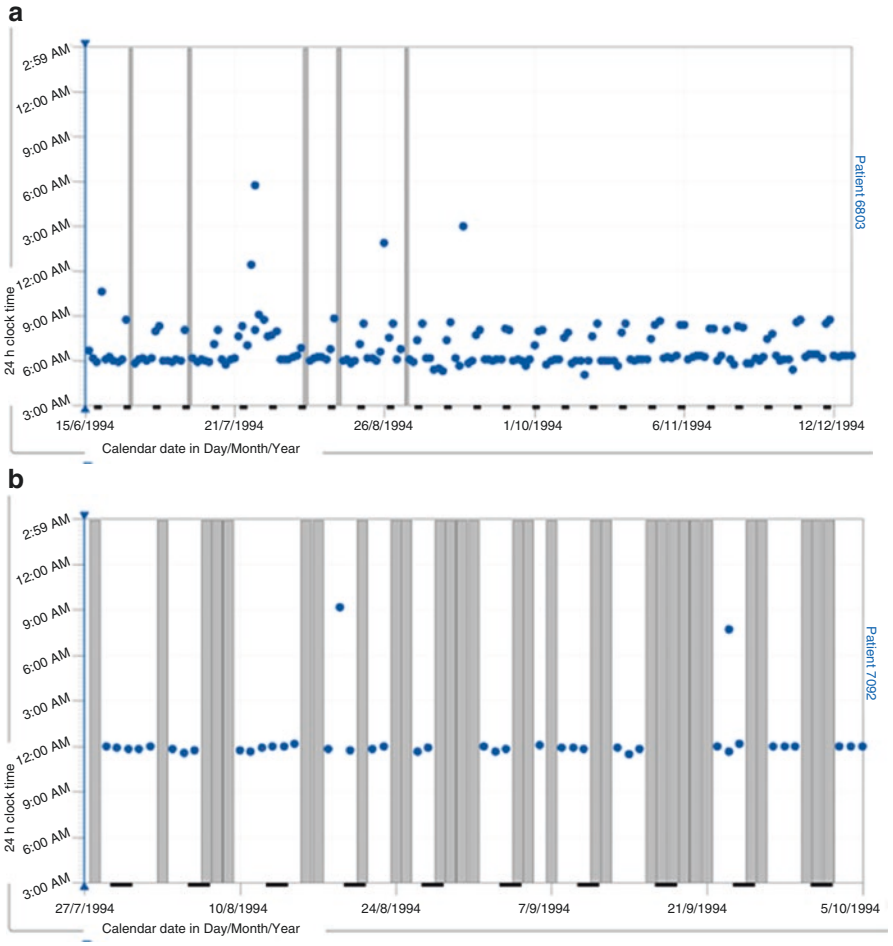


Fig. 3.2 Dosing chronology plots of four patients. Calendar date (dd/mm/yy) is shown on the horizontal axis, and 24-h clock time is shown on the vertical axis. Each blue dot indicates the electronically recorded time and date of dosing. The vertical tan lines depict missed doses. Extended periods without dosing (drug holidays) are shown by vertical tan bars, the width of which reflects the number of days without dosing. Patient A takes the medication around 6:00 am with 2–3 h delays in drug intake on weekends. Patient B takes timely the medication at noon but misses many single and consecutive doses. Patient C takes the medication in the morning between 6:00 am and 11:30 am; there are several single missed doses followed by full treatment discontinuation. Patient D takes the medication in the afternoon, around 3:00 pm; there is a trend in missing more doses as time pass on

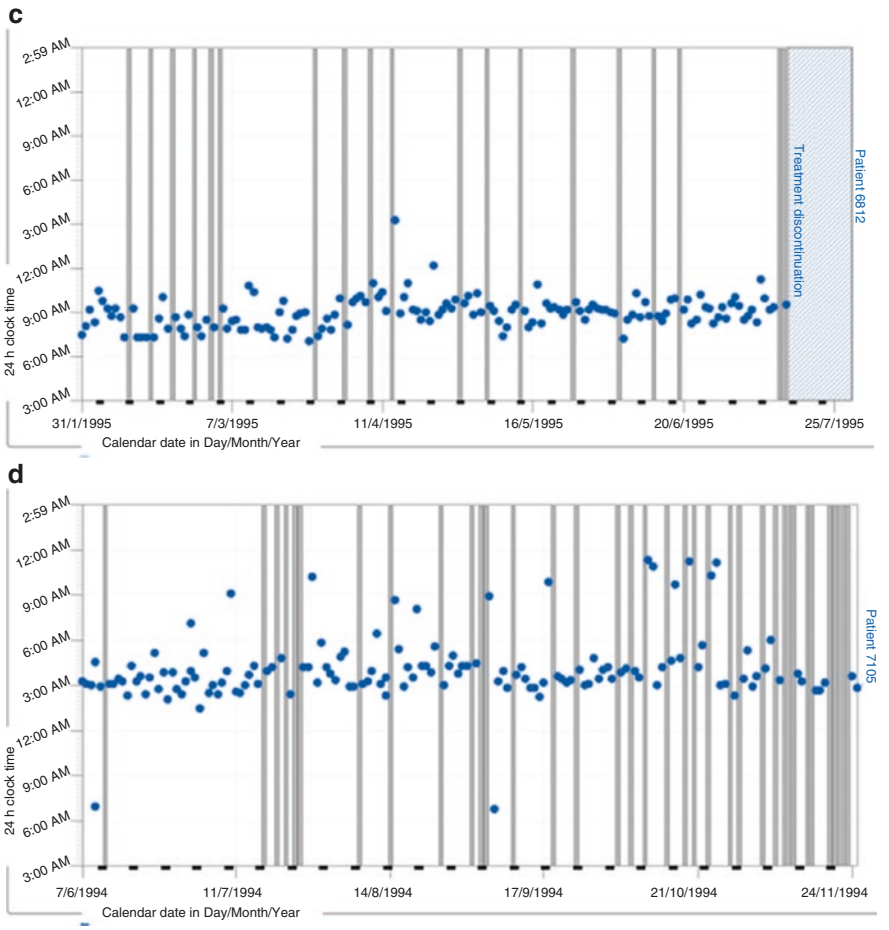


Fig. 3.2 (continued)

shortcoming to summarize medication adherence as a percentage of prescribed drug taken, or worse to dichotomize as adherent versus non-adherent.

The recent hype about ingestible smart sensors, which integrate a microcircuit into an ingestible drug that is then activated by gastric acid, constitutes thus an invasive, cumbersome, and probably expensive way to solve a non-problem in the measurement and management of patient nonadherence. Beside the unresolved long-term safety, there is a high requirement of patient involvement as the patients are required to wear continuously a skin patch which contains an antenna to capture the weak signal that arises from the ingested microchip. This type of approach requires furthermore the need for reformulation, repackaging, new stability studies, and revised labeling claims.

3.3 From Reliable Measure to Effective Interventions

MEMS was originally developed and commercialized to bring an objective, continuous, non-intrusive, affordable, and rich sampled measure of medication adherence. The large amount of dosing history data collected using the MEMS provided strong evidence to distinguish the three key elements of medication adherence which led to the ABC taxonomy [6]: (A) initiation of therapy, (B) implementation of the dosing regimen, and (C) persistence with treatment. Those three elements are typically hidden in the mist and sparseness of pre-electronic measures.

There is now compelling evidence that the combination of the ABC taxonomy, with appropriate measures, and sound analysis allows one to understand and quantify the problem of adherence in each individual patient. This information can, in turn, be used as feedback for a focused discussion between a healthcare provider and the patient. This approach has been proven to be the most effective to enhance medication adherence [7] and optimize therapy [8].

Smart packages enabling electronic monitoring of medication adherence have been around for some time. When looking at a summary of the available literature [9], it is evident that MEMS is, de facto, a gold standard to measure adherence, and that MEMS feedback does improve medication adherence when integrated into care systems. Now, the remaining challenge is how to implement these findings in large-scale clinical practice. There is a need to simplify and accelerate the development of new solutions by bringing together the technical components, like smart packages, connectivity, hosting, and analytics. Integrated and secured platforms will make smarter approaches to adherence a reality.

3.4 "Real-Time": What Does It Mean?

What flashes is not necessarily gold! One should be careful about buzz words like "real-time" without considering the ins and outs of new gimmicks, which are often not scientifically validated. In 1977, the main innovation of electronic monitoring using MEMS is to bring real-time stamping of the dosing events. Since then, the concept of "real-time" has evolved and it is useful to distinguish the following features:

- Real-time **capture** of the dosing events.
- The fundamental principle of electronic monitoring is real-time stamping of the dosing event. The ability to capture the dosing event in real time constitutes the fundamental benefit of electronic monitoring over pre-electronic methods, like pill counting, which can be easily falsified to create the impression of good looking adherence behavior.
- Real-time **transmission** of the dosing events.

- As of today, the transmission of the dosing history data, stored in the smart package, happens at point of care using secured and reliable communication. There are some initiatives to transmit the data in real time using patients' smartphone or sim cards directly embedded in the package. Their limited battery life, uncertain connectivity, and their "best effort" paradigm make them currently incompatible with the requirement of smart patient management and general individualization of care which is "mission critical." No doubt that the evolution of the technology, for example, Internet of Tings (IoT) will facilitate real-time transmission in the future.
- Real-time **feedback** of dose intake/omission.
- With modern technology, it becomes feasible to feedback the patients in real time about a dose that is taken or to remind a dose that has been omitted. While this feature may look attractive, it has not proven to be effective [10]. The first issue is that this approach assumes that the patient has forgotten to take the medication while, in reality, there are more than 700 factors reported to be associated with medication nonadherence [11]. Furthermore, such a system is intrusive for most patients, may induce stigma, and can lead to treatment discontinuation.

There is no doubt that a broader adoption of smart packages will require frictionless connectivity and integration into managed care platforms. Today, there are however technical, legal, and ethical constraints that need to be considered.

Conclusion

Solutions based on smart and connected packaging, which can provide an accurate measure of whether patients are following their treatment regimens, could be the answer to inefficient drug therapies. But they've been held back by the practicalities of storing, analyzing, and exchanging data from thousands of remote devices. That's all changing thanks to more connected and integrated platforms. They are helping to simplify and accelerate the development of new solutions by bringing together the technical components, like devices, connectivity, hosting, and analytics. This will make smarter approaches to adherence a reality.

Once you have better information on adherence, you can start to have an immediate impact on patients' behavior simply by sharing it with them, their relatives, and healthcare providers. Data can be collected, analyzed, and then shared with patients via apps on their smartphones—all, potentially, in near-real time. Sharing data with patients which shows them that they're not following their treatments can provide a stronger impetus for them to improve.

As more data on adherence is collected, it may be possible to send patients increasingly personalized and compelling messages. Instead of just saying "you took eight out of ten tablets today," clinicians may be able to say, "you reduced your chances of getting better by 20%." This reinforces educational material and reminders, and enables clinicians to start putting more onus on patients and their families to own their treatments.

The ultimate objective of smart packages is to bring reliable and rich data on medication adherence which will be transformed into a vital sign to which healthcare professionals and patients routinely attend.

References

1. Paterson DL, Swindells S, Mohr J, Brester M, Vergis EN, Squier C, Wagener MM, Singh N. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med. 2000;133(1):21–30.
2. Dobbels F, De Geest S, van Cleemput J, Droogne W, Vanhaecke J. Effect of late medication non-compliance on outcome after heart transplantation: a 5-year follow-up. J Heart Lung Transplant. 2004;23(11):1245–51.
3. Bhatia S, Landier W, Hageman L, Chen Y, Kim H, Sun CL, Kornegay N, Evans WE, Angiolillo AL, Bostrom B, Casillas J, Lew G, Maloney KW, Mascarenhas L, Ritchey AK, Termuhlen AM, Carroll WL, Wong FL, Relling MV. Systemic exposure to thiopurines and risk of relapse in children with acute lymphoblastic leukemia: a Children's Oncology Group Study. JAMA Oncol. 2015;1(3):287–95. https://doi.org/10.1001/jamaoncol.2015.0245.
4. Blaschke TF, Osterberg L, Vrijens B, Urquhart J. Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories. Annu Rev Pharmacol Toxicol. 2012;52:275–301.
5. Vrijens B, Urquhart J. Methods for measuring, enhancing, and accounting for medication adherence in clinical trials. Clin Pharmacol Ther. 2014;95(6):617–26. https://doi.org/10.1038/clpt.2014.59. Epub 2014 Mar 12.
6. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, Dobbels F, Fargher E, Morrison V, Lewek P, Matyjaszczyk M, Mshelia C, Clyne W, Aronson JK, Urquhart J, ABC Project Team. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol. 2012;73(5):691–705.
7. Demonceau J, Ruppar T, Kristanto P, Hughes DA, Fargher E, Kardas P, De Geest S, Dobbels F, Lewek P, Urquhart J, Vrijens B, ABC Project Team. Identification and assessment of adherence-enhancing interventions in studies assessing medication adherence through electronically compiled drug dosing histories: a systematic literature review and meta-analysis. Drugs. 2013;73(6):545–62.
8. Burnier M, Schneider MP, Chioléro A, Stubi CL, Brunner HR. Electronic compliance monitoring in resistant hypertension: the basis for rational therapeutic decisions. J Hypertens. 2001;19(2):335–41.
9. Vrijens B, Urquhart J, White D. Electronically monitored dosing histories can be used to develop a medication-taking habit and manage patient adherence. Expert Rev Clin Pharmacol. 2014;7(5):633–44.
10. Volpp KG, Troxel AB, Mehta SJ, Norton L, Zhu J, Lim R, Wang W, Marcus N, Terwiesch C, Caldarella K, Levin T, Relish M, Negin N, Smith-McLallen A, Snyder R, Spettell CM, Drachman B, Kolansky D, Asch DA. Effect of electronic reminders, financial incentives, and social support on outcomes after myocardial infarction: the HeartStrong randomized clinical trial. JAMA Intern Med. 2017;177(8):1093–101.
11. Kardas P, Lewek P, Matyjaszczyk M. Determinants of patient adherence: a review of systematic reviews. Front Pharmacol. 2013;4:91.

Measurements of Antihypertensive Medications in Blood and Urine

4

Pankaj Gupta, Prashanth Patel, and Maciej Tomaszewski

4.1 Background

Biochemical screening for non-adherence provides an objective and direct approach to detection of medications in blood or urine. The biochemical analysis is based on high performance liquid chromatography-tandem mass spectrometry (LC-MS/MS). Chromatography was first developed in 1903 by celebrated Russian botanist Mikhail S. Tswett to separate plant pigments [1]. Liquid chromatography is an evolution of this technique and is based on the principle of partition chromatography.

P. Gupta, M.B.
Department of Chemical Pathology and Metabolic Disease,
University Hospitals of Leicester NHS Trust, Leicester, UK

Department of Cardiovascular Sciences, University of Leicester, Leicester, UK

Division of Cardiovascular Sciences, Faculty of Biology, Medicine and Health,
University of Manchester, Manchester, UK
e-mail: Pankaj.Gupta@uhl-tr.nhs.uk

P. Patel
Department of Chemical Pathology and Metabolic Disease,
University Hospitals of Leicester NHS Trust, Leicester, UK

Department of Cardiovascular Sciences, University of Leicester, Leicester, UK
e-mail: Prashanth.patel@uhl-tr.nhs.uk

M. Tomaszewski (✉)
Division of Cardiovascular Sciences, Faculty of Biology, Medicine and Health,
University of Manchester, Manchester, UK

Division of Medicine and Manchester Heart Centre,
Manchester University NHS Foundation Trust,
Manchester Academic Health Science Centre, Manchester, UK
e-mail: Maciej.Tomaszewski@manchester.ac.uk

M. Burnier (ed.), *Drug Adherence in Hypertension and Cardiovascular Protection*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-76593-8_4

The technique "partitions" (or separates) analytes based on differences in solubility in two phases, namely the mobile and stationary phases [2]. The technique was invented by J P Martin and R LM Synge for which they were awarded the Nobel prize in Chemistry in 1952.

Mass spectrometry was first described in 1897 by Sir Joseph J Thomson [3]. A mass spectrometer principally consists of walls made of two pairs of strong magnets (called a quadrupole). Ions travel at variable speed based on their mass (m) to charge (z) ratio and thus are filtered while passing through it. Mass spectrometry was used in research laboratories in the 1960s and 1970s. It expanded dramatically since the ability to volatilise large molecules by electrospray ionisation was achieved (Nobel prize in Chemistry awarded to John Fenn 2002) [4]). The mass spectrometer in the past was interfaced with gas chromatography which required more processing of samples and hence was difficult and time-consuming. Liquid chromatography is a lot simpler and therefore once liquid chromatography was interfaced with the mass spectrometer the use of LC-MS/MS increased exponentially over the last two decades.

LC-MS/MS is now the workhorse and a gold standard technique for a wide range of specialised clinical tests use such as measurement of vitamin D in blood, quantification of steroids such as cortisol or 17-hydroxy progesterone in blood and urine and in proteomics/metabolomics research [5]. Due to its high specificity and sensitivity, LC-MS/MS has been used to detect drugs in forensic laboratories [6] and to detect doping in competitive sports [7].

4.2 Principle of LC-MS/MS

The key components of an LC-MS/MS are outlined schematically in Fig. 4.1.

4.2.1 Sample Derivatisation

A blood or urine specimen contains a complex mixture of substances including proteins, lipids, carbohydrates, cells and numerous small molecules. The sample therefore requires purification by derivatisation. An aqueous aliquot of this derivatised sample is then injected into a high performance liquid chromatograph.

4.2.2 High Performance Liquid Chromatography (HPLC)

HPLC separates the analytes of interest in a specimen by passing it through a fine bore column under high pressure. Hence separation of analytes by HPLC is a much faster process than by normal pressure chromatography. The HPLC column is packed with tiny silica particles that form the stationary phase. Commonly these silica particles are coated with compounds having alkyl side chains to increase their affinity

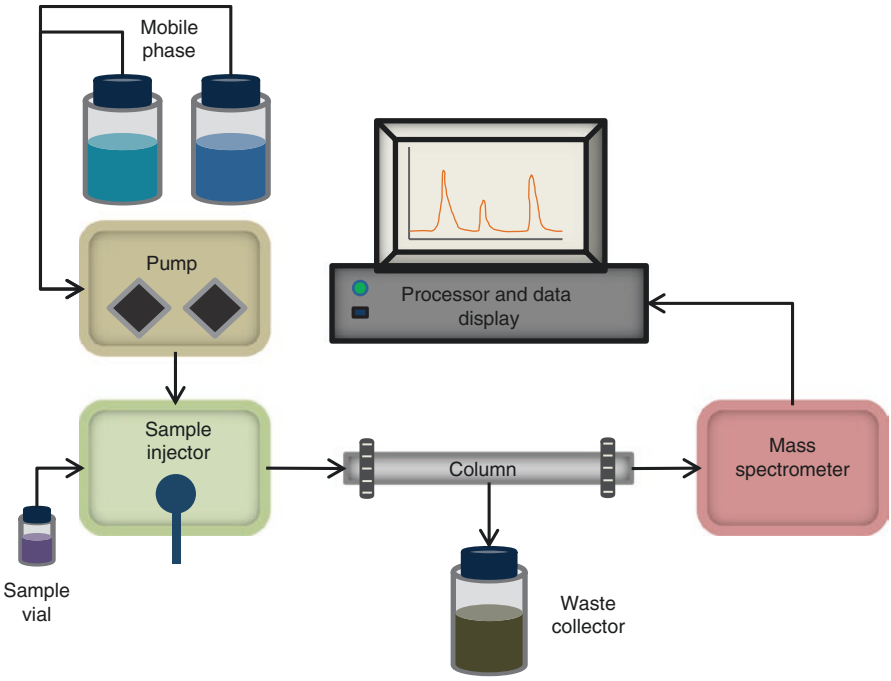


Fig. 4.1 Schematic visualisation of the key components of a high performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) instrument

for hydrophobic compounds. Thus, analytes of interest (which are usually hydrophobic) bind to the stationary phase and are hence separated from the aqueous phase.

The type of column and the alkyl side chain are chosen to provide an optimum internal porosity and retention of the analytes of interest from the mixture of substances present within a specimen. Samples are introduced at one end of the column, the analyte of interest is retained and the rest of the sample is discarded from the column as effluent. The retained analytes are then released or eluted from the column by using specialised solutions and buffers [8].

4.2.3 Mass Spectrometry (Fig. 4.2)

The analytes need to be introduced in the mass spectrometer in a volatised and ionised form so that they can be suitably detected. The two common volatilisation techniques are Atmospheric Pressure Ionisation (API) or ElectroSpray Ionisation (ESI). The separated sample is introduced through a nebuliser under conditions of dry heat or reduced pressure into a narrow inlet which causes them to form small ionised droplets. Once ionised, the sample is fed into the mass spectrometer.

A tandem mass spectrometer (MS/MS) consists of two sequential sets of mass spectrometer that are aligned in tandem and hence the term tandem mass

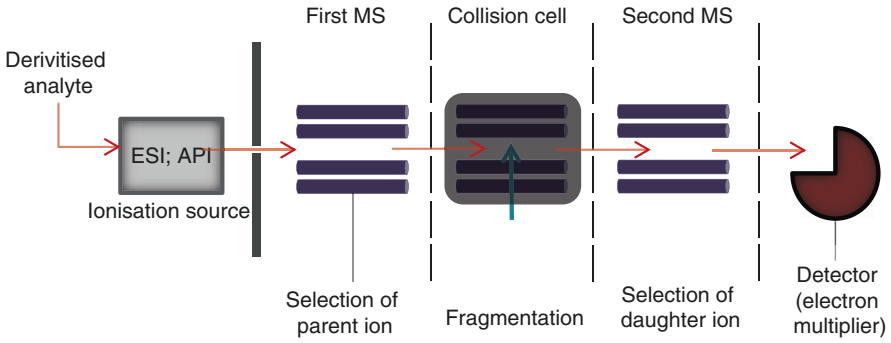


Fig. 4.2 Scheme of the components of a tandem mass spectrometer (MS/MS)

spectrometer. The first mass spectrometer filters ions (called as parent ions) which are introduced in a collision cell forming daughter ions which are again filtered through the second mass spectrometer.

The filtered ions can now be finally detected and then identified. The identification is based on the fragmentation pattern of an analyte. This can be predicted from their structure and previous experience of a laboratory. Thus, most users of LC-MS/MS have a library of analytes with their expected unique identifier ions that is used to identify the analyte of interest. In our laboratory, at least two unique *m*/*z* ions are used to identify a drug and/or its metabolite [8].

In summary, the entire process of LC-MS/MS consists of purification of an analyte and separation by HPLC. The sample is then vaporised and ionised. The ions are fed into the first MS and are filtered by their *m*/*z* ratio. These parent ions then are further fragmented in the second collision cell into daughter ions which are again filtered in the second MS based on their *m*/*z* ratio. The filtered parent and daughter ions can be identified by their unique mass to charge (*m*/*z* ratios).

4.3 The Biochemical Principles of Assessment of Non-adherence to Antihypertensive Treatment

We and others have developed an LC-MS/MS method to detect the most common antihypertensive medications in blood and urine to diagnose non-adherence to blood pressure lowering therapy [9–16]. Most of the modern LC-MS/MS methods can detect presence or absence of antihypertensives reliably with high specificity and extraordinary sensitivity (usually in the nanogram range and typically <10 ng/L) [15]. In our centre, the LC-MS/MS-based system can screen for 40 of the most commonly prescribed antihypertensive medications in a single urine sample [9]. The absence of medications in a sample implies that it has not taken for the time equivalent to at least 4–6 half-lives of the medication. The time of retention of medications in bodily fluids is determined by its pharmacokinetic and pharmacodynamics profile along with a patient's individual metabolic characteristics [17]

Table 4.1 Examples of antihypertensive medications and their 4–6 half-lives

Medication	4–6 Half-lives (hr)
ACE/ARB	
Ramipril	36–108
Lisinopril	48–72
Enalapril	44–152
CCB	
Amlodipine	140–420
Felodipine	44–96
Diltiazem	8–36
Verapamil	20–78
Diuretics	
Indapamide	60–90
Spironolactone	52–108
Furosemide	4–18
Beta blockers	
Bisoprolol	40–72
Atenolol	12–84
Labetalol	12–36
Others	
Clonidine	40–150
Doxazosin	64–132
Prazosin	12–18

ACE/ARBs angiotensin converting enzyme inhibitors/angiotensin receptor blockers, *CCB* calcium channel blockers; data from [17]

(Table 4.1). It has to be appreciated that the biochemical test provides a snapshot of non-adherence and as yet there is no data on how well it reflects long-term persistence with antihypertensive treatment [18] or long-term health outcomes. LC-MS/MS-based analysis is also not immune to changes in patients' behaviour activated by clinical appointments (toothbrush effect or white coat adherence) [19].

4.4 Laboratory Processing of Samples

Biochemical screening for non-adherence can be conducted using a urine or blood sample. Our preference is using a urine sample due to the non-invasive nature of the collection. The volume of urine or blood required is only around 1 mL. The samples are stable for 3–4 days at room temperature and hence can be transported by ordinary post to remote laboratories where LC-MS/MS is available. Our hospital now receives samples from around 25 UK and a few overseas centres. Upon receipt, the samples are stored at −20 °C until analysis, which is undertaken in batches of 20–30 samples two-three times a week.

The analytical process is labour and skill intensive. One batch of samples requires 2 hr of a mid-level laboratory technician's time. The run time for each sample on the LC-MS/MS is approximately 30 min. Each run is repeated and performed in two detection modes. Our screening panel has gradually expanded and we can now detect not only almost all known antihypertensives but 20 other medications

including commonly prescribed hypoglycaemics, statins, anti-arrhythmics and newer oral anticoagulants. The outputs from LC-MS/MS are read by a senior laboratory scientist against an in-house library and then interpreted and signed off by a medical consultant. The ultimate report provides qualitative information of whether the prescribed medication was detected or not in a sample.

The instrument is expensive (around £200,000–250,000). This makes biochemical testing for non-adherence unlikely to be available across the world. The lack of widespread use of direct and objective methods to detect non-adherence may be a reason for the persistent clinical challenges to tackle deviations from prescribed antihypertensive medications [20]. Centres with required expertise and availability of LC-MS/MS instruments should increasingly act as hubs to provide access to the biochemical screening for non-adherence to antihypertensive treatment. Indeed, in Leicester we have set up the first National Centre for Adherence Testing (NCAT) in the UK [21] and so far have analysed over 4000 urine samples.

4.5 Detecting Non-adherence to Antihypertensive Treatment

Biochemical analysis of bodily fluids is one of few direct objective methods to confirm non-adherence to treatment. Subjective methods such as physician's perceptions have poor diagnostic accuracy of around 60% as compared to an objective method [22]. Patient self-reported questionnaires tend to over-report adherence by up to 20% [23] and show poor correlation with cardiovascular outcomes [24]. Pharmacy database records are an objective indirect method to assess non-adherence but suffer from inaccuracies (i.e. outdated medication history) and suboptimal completeness of records [25].

Electronic monitoring devices (EMDs) provide an indirect objective method to assess non-adherence and are available in a variety of forms from simple alarm devices to highly sophisticated systems that register and record each time a medication dispensing device is opened. They can provide a rich amount of data including exact time of a missed dose [26]. The limitations of EMDs are that each device can monitor only a single medication, they are expensive and are bulky to carry. Crucially, opening of a medication dispenser is not the same as ingestion of a pill.

Directly observed therapy (DOT) is based on patient's ingestion of antihypertensive medications under a supervision of clinical staff. It is logistically involved, expensive and requires the patient to attend the hospital for at least half-day plus a dedicated supervision of senior clinical staff. It can also lead to serious clinical complications. One study reported that 25% of seemingly adherent hypertensive patients developed significant hypotension as a result of attending DOT appointment [27].

4.6 Prevalence and Risk Factors of Non-adherence to Antihypertensive Medications: Insights from Biochemical Analysis of Bodily Fluids by HPLC-MS/MS

Non-adherence to antihypertensive medications has been previously estimated at 24–86% mainly by using pharmacy databases [28]. One of the highest rates is reported in patients who underwent renal denervation—nearly 80% had some degree of non-adherence to antihypertensive therapy when biochemical testing was performed [29]. We have recently demonstrated in a large study of approximately 1400 patients from two European countries that the prevalence of non-adherence was between 31.5 and 41.6% [30]. Up to 14.5–24.1% patients were completely non-adherent with their prescribed antihypertensive treatment [30]. Biochemical non-adherence to antihypertensive treatment is inversely related to age with the risk decreasing by nearly 35% with each decade of life [30]. Non-adherence to BP lowering therapy is also higher in women than in men [30]. The most striking risk factor for non-adherence is the number of prescribed antihypertensive medications—each increase in this number increases the risk of non-adherence by around 80% [30]. Furthermore, non-adherence to antihypertensive treatment is associated with the use of diuretics [30].

4.7 Our Clinical Experience

We have routinely been performing biochemical screening for non-adherence in the University Hospitals of Leicester Blood Pressure Clinic since 2011. The process is summarised in Fig. 4.3. In cases where non-adherence is suspected, we request the patient to provide a spot urine sample on the day of their clinic appointment after explaining to them the reasons for doing so. The results of the LC-MS/MS-based urine analysis are discussed with them at their subsequent visits.

The insights provided by the information from the biochemical screening for non-adherence are clinically useful both for doctors and patients. The doctors are provided with much needed confidence to discuss the most appropriate management strategy on non-adherence to antihypertensive treatment based on the objective non-detection of prescribed BP lowering medications. This is particularly important given the evidence that a doctor's training in communication has a significant impact on patient's attitude to adherence [31].

Indeed, the results of the test set the scene for an exploration of barriers to adherence, some of which may be embedded in patient's self-beliefs about the necessity of taking medications and illnesses [32]. Due to the largely asymptomatic nature of hypertension, patients do not always feel that they require taking BP lowering medications on a regular basis. The non-detection of antihypertensive medications in

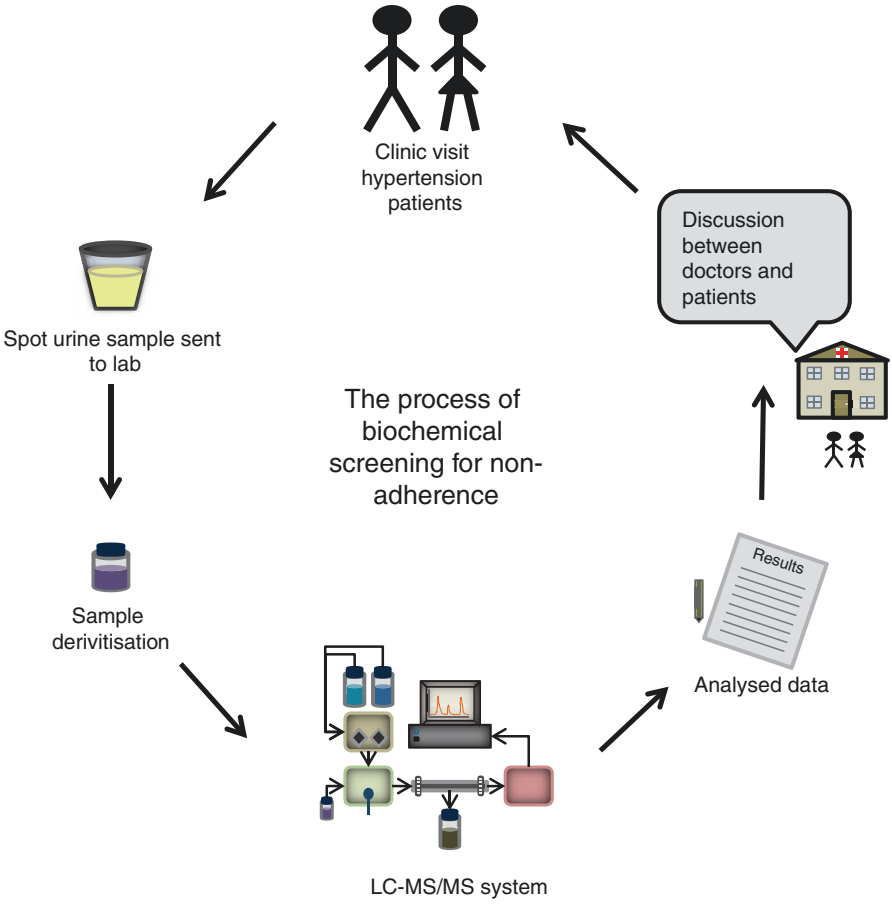


Fig. 4.3 The process of screening for biochemical non-adherence to antihypertensive treatment

urine helps making its linkage to high blood pressure clear to patients over discussion of the results. This discussion shapes the tailored therapy that addresses the key underlying reasons for non-adherence to antihypertensive treatment. Such a personalised approach is the most effective method of improving non-adherence [33]. One of the key reasons for non-adherence to antihypertensive treatment is complex dosing regimes and polypharmacy [30, 34, 35]. Removing unnecessary medications, fixed dose combinations, dosette boxes, involving relatives in reminding the patients to adhere to treatment can be very effective in tackling biochemically confirmed non-adherence to BP lowering therapy. We have also started involving a psychologist to help exploring the complex nature for reasons of intentional non-adherence and have found this approach very useful.

Reassuringly, the patients' acceptance of the biochemical screening for non-adherence to treatment is overwhelmingly very positive. In our experience, it has not led to an erosion of trust or adversely affected the doctor–patient relationship.

We find that biochemical screening for non-adherence is particularly helpful in patients with suspected resistant hypertension and prior to invasive therapeutic procedures such as renal denervation [29, 36]. We proposed that biochemical analysis of urine by LC-MS/MS should be introduced early for uncontrolled hypertension, prior to undertaking expensive, unnecessary tests or treatment escalation [36].

4.8 Other Benefits of Biochemical Testing for Non-adherence to Antihypertensive Treatment

Besides the diagnostic role of LC-MS/MS-based analysis, there is evidence that the repeated screening for non-adherence to antihypertensive treatment helps improving patients' blood pressure control. A small study demonstrated that systolic and diastolic blood pressure on follow-up dropped by around 46 mmHg and 20 mmHg (respectively) in initially non-adherent hypertensive patients [13]. In our clinic, we have noted similar improvements in blood pressure [37]. The test is repeated on subsequent visits and in our experience by the third visit a majority of non-adherent patients become adherent. The test precludes the need to investigate a non-adherent patient unnecessarily or add medications with cost implications to the health economy. A cost–benefit analysis has demonstrated that the test is cost-effective in detection of non-adherence in cases of resistant hypertension [38].

4.9 The Future

Biochemical adherence testing is likely to become embedded in the routine management of patients with difficult to treat hypertension in the near future. It is tempting to foresee the future with the biochemical screening for non-adherence available as a point of care instrument in doctors' consultation room but the technology for this is not currently available. The more likely scenario is that non-biochemical testing for adherence will become available more widely in a few specialised laboratories providing the service for a country or a region. There is no reason why the screening cannot be used in other chronic cardiovascular diseases such as coronary artery disease or heart failure. Further research in the field will, in our view, provide the evidence of the clinical and economic benefits across an array of cardiovascular conditions.

Conclusion

Biochemical screening for non-adherence is a rapidly expanding technique to diagnose non-adherence in the field of hypertension. It is reliable, has been demonstrated to have good diagnostic ability and can be used in busy routine clinical practice. It is especially of use in detecting non-adherence in suspected cases of resistant hypertension when there is a suboptimal response to treatment and prior to any surgical or complex investigations for patients with uncontrolled hypertension. It also helps in treating patients and appears to have therapeutic potential

in control of blood pressure. The test is well accepted by patients and provides confidence to health professionals about a patient's non-adherence status, thus allowing for an objective non-accusatory discussion about the patient's reasons for non-adherence. It is limited in that it only provides non-adherence at a single time point but can be repeated with ease. The use of biochemical screening can be extended to testing for other cardiovascular medications and we anticipate that its use will continue to grow in the future and become an integral part of management of patients with chronic cardiovascular diseases.

Case Study

First Visit

A 42-year-old female hypertensive patient of white European ethnicity was referred to Hypertension Clinic for management of her uncontrolled hypertension by her primary care physician.

She was asymptomatic from the clinical point of view. There was no history of depression or co-morbidities. She was a non-smoker, drank alcohol in moderation and there was no family history of hypertension or premature cardiovascular disease.

On referral, her antihypertensive treatment consisted of five antihypertensive medications including a diuretic—all BP lowering medications were prescribed in maximum tolerated doses. She mentioned her BP had always been difficult to control but denied non-adherence on questioning.

On examination, she had a raised body mass index of 37.8 kg/m^2, a pulse rate of 80 beats per minute and clinic BP of 174/92 mmHg. There were no stigmata of secondary hypertension. Her ECG and urine dipstick analysis were also normal. On routine blood biochemistry, her kidney and thyroid function were normal. On 24 hr ABPM, her average daytime BP was 160/90 mmHg.

A random urine sample was collected for biochemical screening for non-adherence to antihypertensive treatment. The results of her initial LC-MS/MS-based urine analysis are shown below.

PRESCRIBED DRUG	RESULT
LOSARTAN	NOT DETECTED
AMLODIPINE	NOT DETECTED
INDAPAMIDE	NOT DETECTED
DOXAZOSIN	NOT DETECTED
BISOPROLOL	NOT DETECTED

Second Visit

The results of her biochemical analysis of urine were discussed with the patient. She confessed to "forgetting her medications". It was agreed to reduce

the burden of polypharmacy and restart her antihypertensive therapy initially with one medication (Losartan).

Third Visit (6 Months)
Her clinic BP was recorded at 140/86 mmHg and her average BP on 7-day home-based BP monitoring was 129/79 mmHg. The results of the biochemical screening for non-adherence to antihypertensive treatment are shown below:

PRESCRIBED DRUG	RESULT
LOSARTAN	DETECTED

Acknowledgment The authors are grateful to Dan Lane in the Department of Chemical Pathology and Metabolic Disease, Leicester Royal Infirmary who prepared the illustrations used in this chapter. Our work on adherence is supported by British Heart Foundation Clinical Study (CS/17/3/32799).

References

1. Hesse G, Weil H. Michael Tswett's first paper on chromatography. Eschwege: M. Woelm; 1954.
2. IUPAC. Compendium of chemical terminology, 2nd ed. (the "Gold Book"). Compiled by McNaught AD, Wilkinson A. Oxford: Blackwell Scientific Publications; 1997. XML on-line corrected version: http://goldbook.iupac.org (2006-) created by M. Nic, J. Jirat, B. Kosata; updates compiled by A. Jenkins. ISBN 0–9678550–9-8. 2014; https://doi.org/10.1351/goldbook. Accessed 4 Sept 2017.
3. Thomson J. On the cathode rays. Proc Camb Philos Soc. 1897;9:243–4.
4. Fenn JB, Mann M, Meng CK, Wong SF, Whitehouse CM. Electrospray ionization for mass spectrometry of large biomolecules. Science. 1989;246:64–71.
5. Grebe SK, Singh RJ. LC-MS/MS in the clinical laboratory—where to from here? Clin Biochem Rev. 2011;32:5–31.
6. Mbughuni MM, Jannetto PJ, Langman LJ. Mass spectrometry applications for toxicology. EJIFCC. 2016;27:272–87.
7. WADA. Minimum criteria for chromatographic mass spectrometric confirmation of the identity of analytes for doping control purpose (TD2015IDCR). 2015. www.wada-ama.org/sites. Accessed 4 Aug 2017.
8. Pitt JJ. Principles and applications of liquid chromatography-mass spectrometry in clinical biochemistry. Clin Biochem Rev. 2009;30:19–34.
9. Tomaszewski M, White C, Patel P, Masca N, Damani R, Hepworth J, et al. High rates of non-adherence to antihypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis. Heart. 2014;100:855–61.
10. Jung O, Gechter JL, Wunder C, Paulke A, Bartel C, Geiger H, et al. Resistant hypertension? Assessment of adherence by toxicological urine analysis. J Hypertens. 2013;12:766–74.
11. Strauch B, Petrak O, Zelinka T, Rosa J, Somloova Z, Indra T, et al. Precise assessment of noncompliance with the antihypertensive therapy in patients with resistant hypertension using toxicological serum analysis. J Hypertens. 2013;31:2455–61.

12. Ceral J, Habrdova V, Vorisek V, Bima M, Pelouch R, Solar M. Difficult-to-control arterial hypertension or uncooperative patients? The assessment of serum antihypertensive drug levels to differentiate non-responsiveness from non-adherence to recommended therapy. Hypertens Res. 2011;34:87–90.
13. Brinker S, Pandey A, Ayers C, Price A, Raheja P, Arbique D, et al. Therapeutic drug monitoring facilitates blood pressure control in resistant hypertension. J Am Coll Cardiol. 2014;63:834–5.
14. Ewen S, Meyer MR, Cremers B, Laufs U, Helfer AG, Linz D, et al. Blood pressure reductions following catheter-based renal denervation are not related to improvements in adherence to antihypertensive drugs measured by urine/plasma toxicological analysis. Clin Res Cardiol. 2015;104:1097–105.
15. Lawson AJ, Shipman KE, George S, Dasgupta I. A novel 'dilute-and-shoot' liquid chromatography-tandem mass spectrometry method for the screening of antihypertensive drugs in urine. J Anal Toxicol. 2016;40:17–27.
16. Schmieder RE, Ott C, Schmid A, Friedrich S, Kistner I, Ditting T, et al. Adherence to antihypertensive medication in treatment-resistant hypertension undergoing renal denervation. J Am Heart Assoc. 2016;12:5. https://doi.org/10.1161/JAHA.115.002343.
17. Moffat A, Osselton D, Widdop B, Watts J. Clarke's analysis of drugs and poisons. 4th ed. London: Pharmaceutical Press; 2011.
18. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol. 2012;73:691–705.
19. Chatterjee JS. From compliance to concordance in diabetes. J Med Ethics. 2006;32:507–10.
20. Olsen MH, Angell SY, Asma S, Boutouyrie P, Burger D, Chirinos JA, et al. A call to action and a lifecourse strategy to address the global burden of raised blood pressure on current and future generations: the Lancet Commission on hypertension. Lancet. 2016;388:2665–712.
21. NCAT. National Centre for Adherence Testing. 2017. www.leicestershospitals.nhs.uk/aboutus/departments-services/pathology/clinical-biochemistry/national-centre-for-drug-adherence-testing-ncat/. Accessed 4 Aug 2017.
22. Meddings J, Kerr EA, Heisler M, Hofer TP. Physician assessments of medication adherence and decisions to intensify medications for patients with uncontrolled blood pressure: still no better than a coin toss. BMC Health Serv Res. 2012;12:270–6963.
23. El Alili M, Vrijens B, Demonceau J, Evers SM, Hiligsmann M. A scoping review of studies comparing the medication event monitoring system (MEMS) with alternative methods for measuring medication adherence. Br J Clin Pharmacol. 2016;82:268–79.
24. Krousel-Wood M, Holt E, Joyce C, Ruiz R, Dornelles A, Webber LS, et al. Differences in cardiovascular disease risk when antihypertensive medication adherence is assessed by pharmacy fill versus self-report: the Cohort Study of Medication Adherence among Older Adults (CoSMO). J Hypertens. 2015;33:412–20.
25. Chan KS, Fowles JB, Weiner JP. Review: electronic health records and the reliability and validity of quality measures: a review of the literature. Med Care Res Rev. 2010;67:503–27.
26. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. BMJ. 2008;336:1114–7.
27. Hameed MA, Tebbit L, Jacques N, Thomas M, Dasgupta I. Non-adherence to antihypertensive medication is very common among resistant hypertensives: results of a directly observed therapy clinic. J Hum Hypertens. 2016;30:83–9.
28. Chowdhury R, Khan H, Heydon E, Shroufi A, Fahimi S, Moore C, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. Eur Heart J. 2013;34:2940–8.
29. de Jager RL, de Beus E, Beeftink MM, Sanders MF, Vonken EJ, Voskuil M, et al. Impact of medication adherence on the effect of renal denervation: the SYMPATHY trial. Hypertension. 2017;69:678–84.
30. Gupta P, Patel P, Štrauch B, Lai FY, Akbarov A, Maresova V, et al. Risk factors for non-adherence to antihypertensive treatment. Hypertension. 2017;69:1113–20.

31. Zolnierek KB, Dimatteo MR. Physician communication and patient adherence to treatment: a meta-analysis. Med Care. 2009;47:826–34.
32. Horne R, Chapman SC, Parham R, Freemantle N, Forbes A, Cooper V. Understanding patients' adherence-related beliefs about medicines prescribed for long-term conditions: a meta-analytic review of the Necessity-Concerns Framework. PLoS One. 2013;8:e80633.
33. Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, et al. Interventions for enhancing medication adherence. Cochrane Database Syst Rev. 2014;11:CD000011.
34. World Health Organisation. Adherence to long-term therapies: evidence for action. 2003. www.who.int/chp/knowledge/publications/adherence_full_report.pdf. Accessed 12 Dec 2016.
35. Schroeder K, Fahey T, Ebrahim S. Interventions for improving adherence to treatment in patients with high blood pressure in ambulatory settings. Cochrane Database Syst Rev. 2004;2:CD004804.
36. Patel P, Gupta PK, White CM, Stanley AG, Williams B, Tomaszewski M. Screening for non-adherence to antihypertensive treatment as a part of the diagnostic pathway to renal denervation. J Hum Hypertens. 2016;30:368–73.
37. Gupta P, Patel P, Štrauch B, Lai FY, Akbarov A, Gulsin GS, Beech A, Marešová V, Topham PS, Stanley A, Thurston H, Smith PR, Horne R, Widimský J, Keavney B, Heagerty A, Samani NJ, Williams B, Tomaszewski M. Biochemical screening for nonadherence is associated with blood pressure reduction and improvement in adherence. Hypertension. 2017;70:1042–8.
38. Chung O, Vongpatanasin W, Bonaventura K, Lotan Y, Sohns C, Haverkamp W, et al. Potential cost-effectiveness of therapeutic drug monitoring in patients with resistant hypertension. J Hypertens. 2014;32(12):2411–21.

5 Adherence to Antihypertensive and Cardiovascular Preventive Treatment: The Contribution of the Lombardy Database

Giuseppe Mancia, Federico Rea, and Giovanni Corrao

Randomized trials represent the best approach to the investigation of the effectiveness of treatment either compared to placebo or to conventional therapeutic strategies. In contrast, they do not allow to suitably assess another aspect of treatment that is of major importance for patients' protection, i.e. adherence to the prescribed treatment regimen [1]. This is because in trials patients' awareness to be under observation can substantially modify their behaviour [2]. It is also because in trials patients are followed closely, pressurized to abide with no changes by the planned treatment sequence and more effectively motivated to assume to prescribed drug, leading to adherence levels much greater than in the medical practice. This is documented by the studies on adherence derived from trials in which comparison is usually made between groups with adherence levels above and below 80% of the entire prescription time [3], a cut-off value unconceivable in medical practice in which the prevailing adherence to treatment is usually much lower.

This chapter will focus on real-life adherence to antihypertensive drug treatment based on the data obtained over the past 10 years in the population of Lombardy, a region of northern Italy with ten million people. In Italy, clinical examinations, medical visits, and hospitalizations are totally or largely free of charge for all citizens. This is true also for antihypertensive, lipid lowering, and antidiabetic drugs (as well as for other life-saving medicaments) which the patient can obtain from the pharmacist with a physician's prescription. In order to be reimbursed, pharmacists

G. Mancia (✉)
University of Milano-Bicocca, Milan, Italy

Policlinico di Monza, Monza, Italy
e-mail: giuseppe.mancia@unimib.it

F. Rea · G. Corrao
Division of Biostatistics, Epidemiology and Public Health, Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Milan, Italy
e-mail: f.rea@campus.unimib.it; giovanni.corrao@unimib.it

M. Burnier (ed.), *Drug Adherence in Hypertension and Cardiovascular Protection*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-76593-8_5

have to file the prescription to the Public Health Service offices, which allows data to be analysed centrally and adherence to be quantified as (1) treatment discontinuation, i.e. failure to renew a prescription for a prolonged time interval and (2) overall adherence rate, i.e. the ratio between the time covered by prescriptions and the overall follow-up time, which the Lombardy database allows to extend to several years. This "prescription refill" method may overestimate adherence because drug prescriptions do not necessarily mean drug assumption. It has the advantage, however, that data can be obtained in people unaware of being under observation, which means that the results are not distorted by alterations of patients' behaviour or of the variable standard of doctor–patient relationship. In addition, the extended follow-up allows not only to suitably investigate the relationship of adherence to treatment and outcomes but also to measure adherence in a time integrated fashion, thereby taking into account the variable nature of this phenomenon over time. This is a major limitation of the direct methods to assess adherence (drug concentration in urine or plasma and witnessing of drug intake), which are confined to one or few days only, disregarding that adherence in those days does not guarantee adherence during other treatment periods [4].

5.1 Adherence to Drug Treatment in Hypertension

In 445,356 patients from the Lombardy database who received no antihypertensive drug prescription in the preceding 2 years, were prescribed a single antihypertensive drug and were followed for several subsequent years one or more episodes of no renewal of antihypertensive drug prescription for a prolonged time (3 or more months) amounted to more than 60% [5]. Discontinuation was more common during the first year of treatment, but it continued less steeply throughout the entire follow-up.. As shown in Table 5.1, overall, the percentage of patients covered by prescription for more than 50% of the follow-up time was low in all cohorts examined, regardless the differences in age and duration of the follow-up, namely the percentage of patients with a prescription coverage greater than 75% was alwlays <50% and in one cohort <25% [6–8]. Thus, in real life, prolonged discontinuation of antihypertensive drug treatment is an extremely common phenomenon. It is also

Table 5.1 Adherence with antihypertensive drug therapy in three cohorts of patients under antihypertensive drug treatment

Adherence with antihypertensive therapy[a]	[1]	[2]	[3]
Very low	61,690 (25%)	1283 (41%)	7495 (20%)
Low	54,558 (23%)	405 (13%)	6498 (17%)
Intermediate	67,494 (28%)	432 (14%)	8256 (21%)
High	58,852 (24%)	990 (32%)	16,212 (42%)

[a]Patients were newly treated hypertensive. Adherence was measured according the proportion of days covered by antihypertensive drug prescription with respect to the days of follow-up. Data were obtained from patients aged 18 years or more, 40–80 years, and above 70 years, respectively. Duration of follow-up was different in the different cohorts categories of adherence were: very low: ≤25%; low: 26–50%; intermediate: 51–75%; and high: >75% (From [6–8])

common for patients of all ages to remain without antihypertensive drug treatment for a substantial portion of their life.

5.2 Adherence and Type of Initial Antihypertensive Monotherapy

As shown in Fig. 5.1, in the previously mentioned large patients cohort [5] discontinuation of initial antihypertensive monotherapy varied markedly according to the class of the initial drug prescribed. Confirming previous evidence, the risk of discontinuation was maximal when a diuretic was initially prescribed, followed by a beta-blocker, an alpha-blocker, a calcium channel blocker, an ACE inhibitor, and an angiotensin receptor antagonist. The difference between diuretic and beta-blockers on one side, and blockers of the renin-angiotensin system on the other was marked, whereas that between the two RAS blockers was small, i.e. only 8% [5]. Similar findings were obtained in a similarly large cohort ($n = 433{,}680$) addressed few years later, in which drug treatment discontinuation between ACE inhibitor and angiotensin receptor antagonists was even less, i.e. 5% [9], at variance from trial data which have reported a much greater difference between ACE inhibitor and angiotensin receptor antagonist treatment [10–12]. This implies that when combination treatment is prescribed (two drugs combinations, three drug combinations, or the polypill) the risk of treatment discontinuation may be dominated by the inclusion of a diuretic, whereas the choice between inclusion of an ACE inhibitor or an angiotensin receptor antagonist may have much less importance.

A question which has rarely been addressed is whether, within any class, drugs show similar or different treatment discontinuation rates. Our data [13] show that, within classes, all drugs, except angiotensin receptor antagonists, differ markedly.

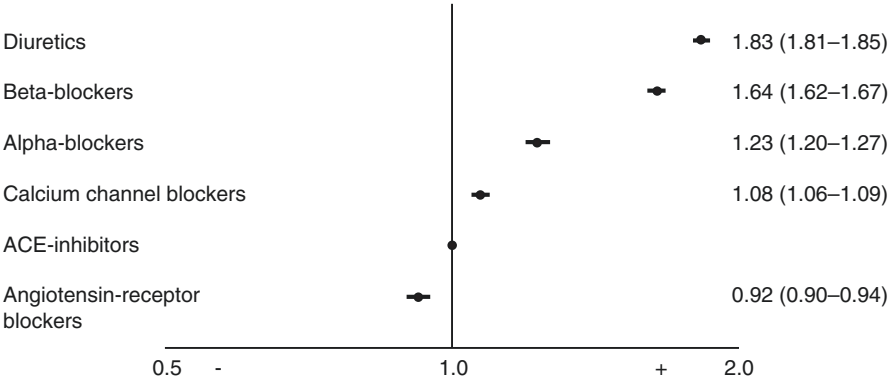


Fig. 5.1 Relative risk of discontinuing initially prescribed monotherapy in patients of Lombardy in whom no antihypertensive drug prescription had been issued in the preceding 2 years. Data from 445,356 in whom the initially prescribed drug was a diuretic, a beta-blocker, an alpha-blocker, a calcium channel blocker, an ACE inhibitor (ACEI), or an angiotensin receptor antagonists. Patients' follow-up was 1 year (Modified from [5], with permission)

Namely, treatment discontinuation varies to a pronounced degree between different diuretics, calcium channel blockers, beta-blockers, and ACE inhibitors, whereas it is superimposable between angiotensin receptor antagonists except for losartan, for which discontinuation rate was found to be about 40% greater than that of all germane drugs (Fig. 5.2).This means that, when considering an aspect of treatment such discontinuation of the prescribed therapy, reference to individual drugs rather than drug classes is more appropriate. Interestingly, in a comparison between generic and brand-name drugs no difference in discontinuation rate was found, this being the case both when (1) patients taking the former or the latter drugs were confronted and (2) confrontation was based on subperiods of the follow-up within patients, i.e. subperiods in which they were taking generics were compared with subperiods in which they were taking the corresponding brand-name agents. The latter approach eliminated the potential confounding effect of between-patient differences in clinical characteristics as cause of the results(Fig. 5.3) [14].

5.3 Factors Involved in Adherence to Antihypertensive Drugs

Figure 5.4 summarizes the factors that in real life were found to affect discontinuation of antihypertensive drug treatment [9]. Discontinuation was not substantially affected by age and, at variance from a number of previous studies, was greater in females than in males. It was not affected by the concomitant prescription of lipid lowering agents, reduced by the concomitant prescription of antidiabetic drugs and clearly increased by the concomitant prescription of antidepressant agents. Discontinuation of antihypertensive agents was also less in patients with hospitalizations with cardiovascular or renal disease in the previous years (probably because of patients' greater awareness of the importance to achieve BP control) whereas it was more frequent in patients with previous hospitalizations for rheumatic diseases, respiratory diseases or cancer, probably because under these circumstances antihypertensive treatment was not priorital compared to the treatment of conditions more markedly affecting well-being and polarizing patient's concern. As expected, treatment discontinuation was highest in patients having a hospital diagnosis of dementia. This suggests that in this condition prescriptions of cardiovascular risk factors may be followed by limited implementation, and thus perhaps by reduced effectiveness.

An unexpected finding was that the discontinuation rates were greater in large Lombardy cities and that overall they shared a significant relationship with the population density of the place where patients lived (Fig. 5.5), a density greater than 3004 people per km^2 showing an about 18% greater rate of discontinuing treatment compared to a density of <154 people per km^2 [9]. A reasonable speculation may be that lower population densities reduced the difficulty of people to be visited by (or meet) a doctor and by and large favour a better doctor–patient relationship. On a more general ground, it should be emphasized that analysing adherence to treatment in different geographical areas may represent an important tool for health authorities to detect and act to solve this therapeutic problem where it appears to be greater.

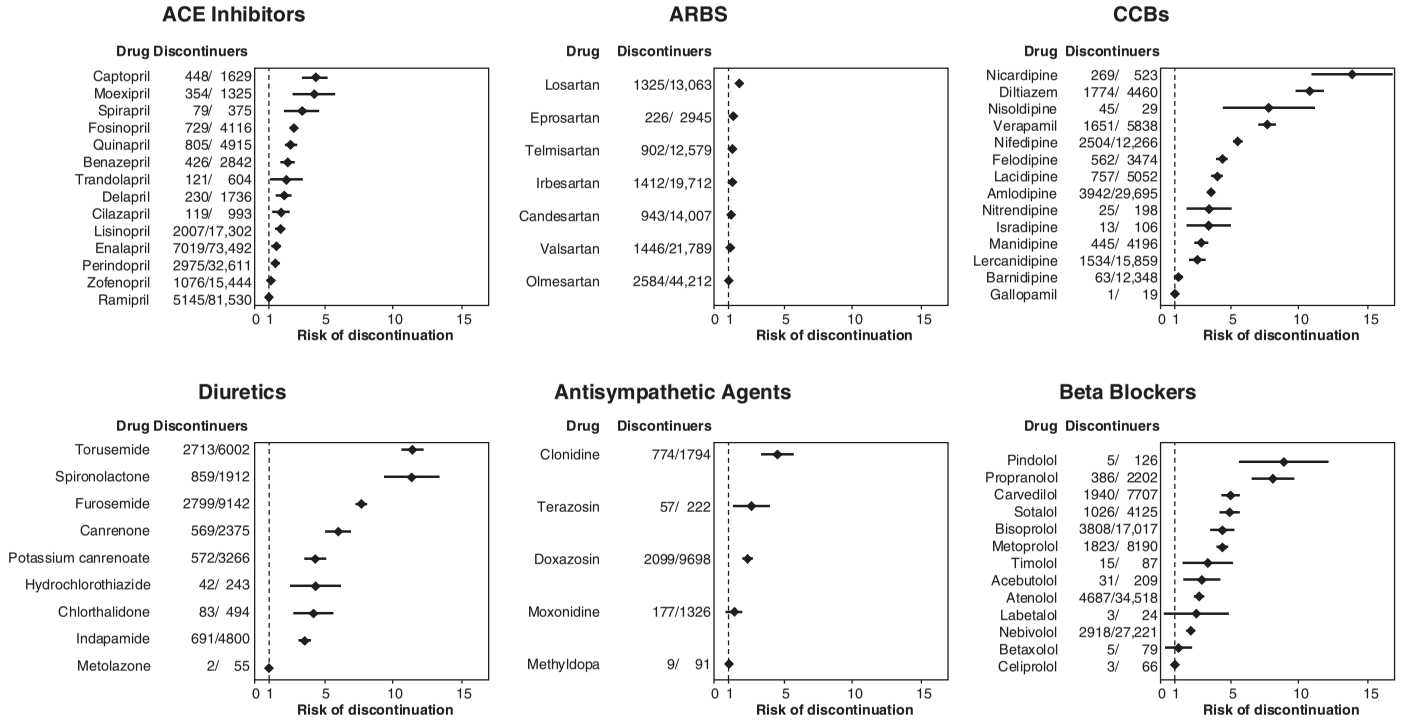


Fig. 5.2 Relative risk of discontinuing initially prescribed monotherapy for all individual drugs within major drug classes available in Italy. Data from patients of Lombardy in whom no prescription had been issued in the preceding years. *ARB* angiotensin receptor antagonist, *CCB* calcium channel blocker (from [10], with permission)

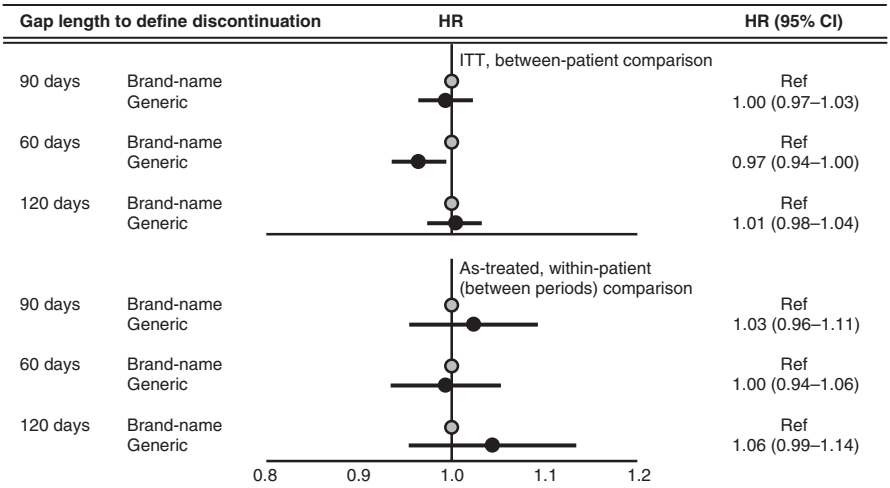


Fig. 5.3 Relative risk of discontinuation of initial antihypertensive drug monotherapy with a generic or a brand-name agent. Data from 101,618 patients. Discontinuation was defined as failure to renew antihypertensive drug prescription for ≥90 days, ≥ 60 days or ≥120 days. In the upper part, data are shown as comparisons between patients on an intention-to-treat basis (ITT). In the lower part, they are shown as within-patients comparisons, i.e. comparisons of subperiods of the follow-up in which patients were prescribed a generic vs. those in which they were prescribed the corresponding brand-name agent. The latter approach eliminates the confounding effect of between-patients differences as cause of the results. Data are shown by taking initial treatment with a brand-name drug as reference (from [11], with permission)

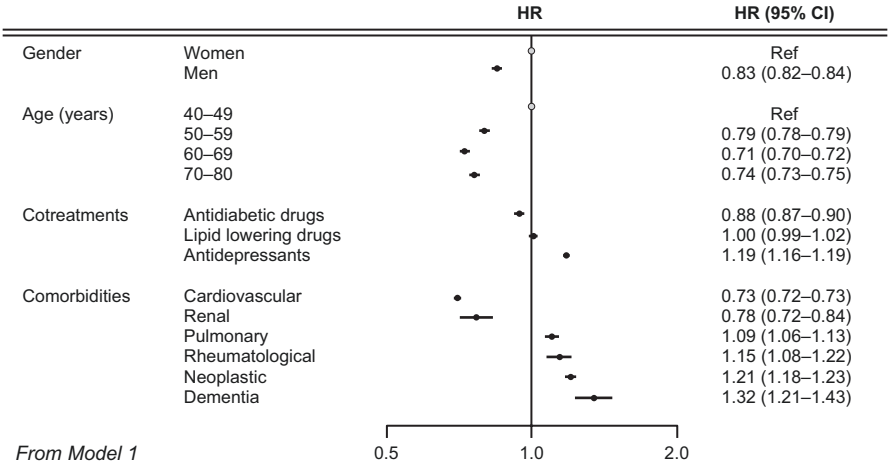


Fig. 5.4 Risk of discontinuation of initial antihypertensive drug monotherapy according to demographic variables, co-treatments, previous hospitalization for cardiovascular, renal, respiratory, rheumatic diseases, cancer, or dementia (from [6], with permission)

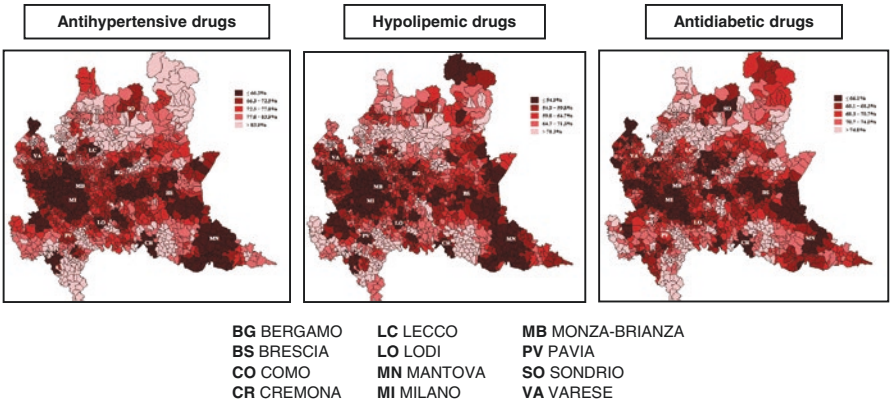


Fig. 5.5 Rate of discontinuation of antihypertensive, lipid lowering, and antidiabetic drug treatment in the Lombardy region according to population density. Data are shown on a colorimetric scale

5.4 Adherence to Treatment and Cardiovascular Risk

Several studies have shown that adherence to antihypertensive drug treatment is associated with greater cardiovascular protection [3, 6–8]. In Lombardy, this was examined by linking the adherence database with a database reporting hospitalizations throughout the region. In a database that included 12,016 hospitalizations, antihypertensive drug discontinuation was found to be accompanied by an almost 37% greater incidence of hospitalization for coronary or cerebrovascular events, the risk of which exhibited a decrease as adherence increased from <25% to ≥75% of the follow-up covered by prescription (Fig. 5.6, left panel) [6]. Similar results were obtained when hospitalization for heart failure was examined (Fig. 5.6, right panel) [7] leaving no question as to the relationship between adherence to antihypertensive drug prescription and cardiovascular protection. Indeed, this was clearly documented also in elderly (age 60–84 years) and very elderly patients (≥85 years of age, average 90 years) in whom an increase in adherence from <25 to ≥75% of the follow-up time was in either case accompanied by a reduction in the risk of cardiovascular events, as assessed by hospital diagnosis (− 14% and – 34%, respectively) (Fig. 5.7) [8]. The reduction was more evident for all-cause mortality (−46% and 47%) and included both stroke and heart failure whereas it was in both groups not significant for myocardial infarction [8]. It should be emphasized that randomized outcome trials are only available in hypertensive patients aged up to slightly above 80 years of age, with an average of 83 years in the HYVET trial [18]. The association between an increased adherence to antihypertensive drugs and cardiovascular protection in patients aged above 85 and 90 years thus represents evidence, albeit of an only observational nature, that the benefit of BP lowering interventions is likely to extend to extremely advanced age strata. This is clinically relevant because

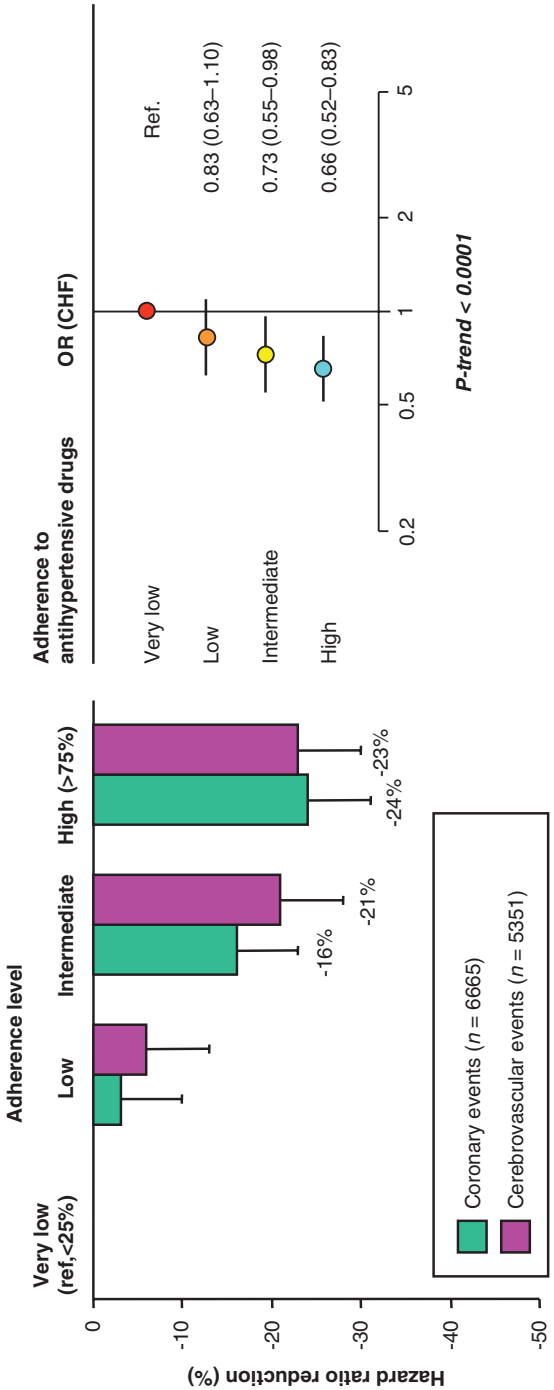


Fig. 5.6 Relationship between adherence to antihypertensive drug treatment and risk of hospitalization for coronary or cerebrovascular events (left panel) and heart failure (right panel). Adherence is categorized from very low to high, i.e. from 25 to ≥75% of the follow-up time covered by prescription (from [15] and [16], with permission)

PDC	Case *n* (%)	Control *n* (%)	OR (95% CI)
Elderly patients: 70-84ys			
0 – 25 %	1571 (19%)	7106 (17%)	Ref.
25 – 50 %	1495 (18%)	6841 (17%)	0.99 (0.92–1.07)
50 – 75 %	1749 (22%)	8527 (21%)	0.93 (0.87–1.01)
75 – 100 %	3363 (41%)	18,416 (45%)	0.86 (0.80–0.92)
Total	8178 (100%)	40,890 (100%)	*p*-trend <0.001
Very elderly patients: ≥85ys			
0 – 25 %	390 (30%)	1317 (24%)	Ref.
25 – 50 %	309 (24%)	1119 (21%)	0.93 (0.78–1.11)
50 – 75 %	273 (21%)	1145 (21%)	0.83 (0.69–1.00)
75 – 100 %	317 (25%)	1814 (34%)	0.66 (0.55–0.79)
Total	1289 (100%)	5395 (100%)	*p*-trend <0.001

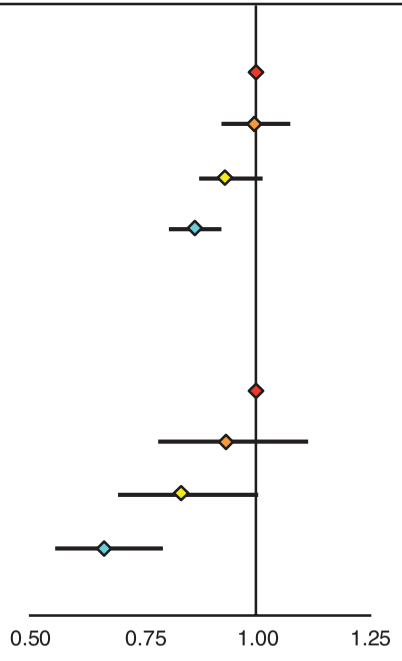


Fig. 5.7 Relationship between adherence to antihypertensive drug treatment and risk of hospitalization for cardiovascular events (myocardial infarction, stroke, heart failure) in patients aged 60–84 or 85 years and beyond. For explanations, see Fig. 5.6 (from [17], with permission). Data taken from European cardiovascular disease statistics 2008

octogenarians and nonagenarians represent a rapidly expanding fraction of the population which is often given many cardiovascular drugs, with no documentation of their protective effect.

5.5 Combination Treatment

The Lombardy database has also been examined for the effect on treatment discontinuation of treatment initiation with combinations of drugs. The results showed that, compared to initial monotherapy (all drugs pooled), treatment initiation with two drugs was accompanied by a marked reduction in the risk of treatment discontinuation with the following year, regardless whether the drugs were taken separately or in a single pill format [9]. They further showed that this advantage was evident when the comparison was done between combinations (1) including a diuretic and diuretic monotherapy and (2) combinations without a diuretic and a monotherapy other than a diuretic [9, 19]. This may provide an explanation for the evidence that initial combination treatment is accompanied by a much better long-term blood pressure (BP) reduction than initial monotherapy [20], despite the therapeutic obligation for the latter approach to add drugs to the initial single drug prescription in order for most patient to reach BP control [21]. It may also provide an explanation for the evidence that, in line with a better long-time BP control, initial combination treatment may lead to a lower long-term risk of cardiovascular events [22, 23]. In the Lombardy database, this was documented by the observation that patients starting and continuing antihypertensive treatment with a combination had a significantly lower risk of cardiovascular outcomes than patients exposed to other treatment strategies, such as initial mono followed by combination therapy, monotherapy throughout and combination therapy down titrated to monotherapy later [24]. Adherence to treatment studies have thus given a contribution to the growing evidence of the advantages of treatment initiation with two drugs, which is now supported also by hypertension guidelines more strongly than in the past.

5.6 Adherence and Other Cardiovascular Drugs

A large body of evidence exists that patients adherence with lipid lowering and antidiabetic drugs is as bad as to antihypertensive drugs and that thus poor adherence to treatment affects cardiovascular prevention as a whole. In the Lombardy database, this was documented by (1) the high rate of discontinuation of statin treatment as well as the evidence that in the majority of the patients the time covered by

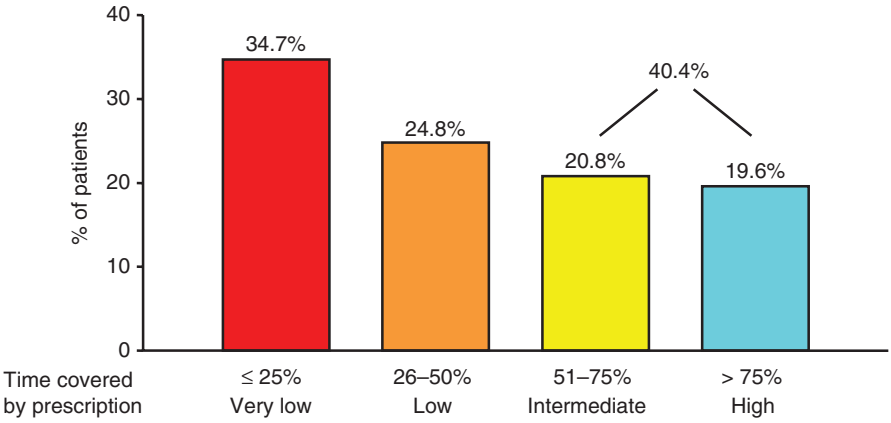


Fig. 5.8 Time covered by statin prescription with respect to the overall follow-up time in the Lombardy database (from [25], with permission)

statin prescription was <50% of the overall follow-up (Fig. 5.8) [25] with no substantial difference (unlike antihypertensive drugs) between the statins prescribed and no differential protective effect between generic and brand-name agents, similarly to antihypertensive drugs [26] and (2) patients failing to renew the first prescription were a high percentage (about one third) of the examined cohort for all three drug treatments, i.e. antihypertensive, lipid lowering, and antidiabetic drugs [27]. It was further shown, in line with other data (3) that also adherence to statin treatment provides coronary protection [25], an observation that was expanded to show that higher adherence to statin leads also to a reduced incidence of hospitalized dementia [28] presumably because most dementia cases may either originate from ischemic brain damage or have a clinically relevant vascular component.

Analysis of adherence to treatment in the Lombardy database also highlighted a phenomenon shown in previous studies but rarely emphasized, namely that greater adherence leads to an increased number of side effects or that it can even increase outcome in case of harmful rather than protective treatments [12]. In our patients, increased adherence to statin treatment progressively increased the risk of developing diabetes (shown by the prescription of antidiabetic drugs at various times after the initiation of statin treatment) (Fig. 5.9) [29]. This is a well-known inconvenience of statin administration with a still unclear mechanistic explanation, which may reduce the benefit of greater adherence to statin administration. The extent of the reduction will have to be calculated after a better information on the adverse prognostic value of the statin-induced vs. native or spontaneous diabetes becomes available.

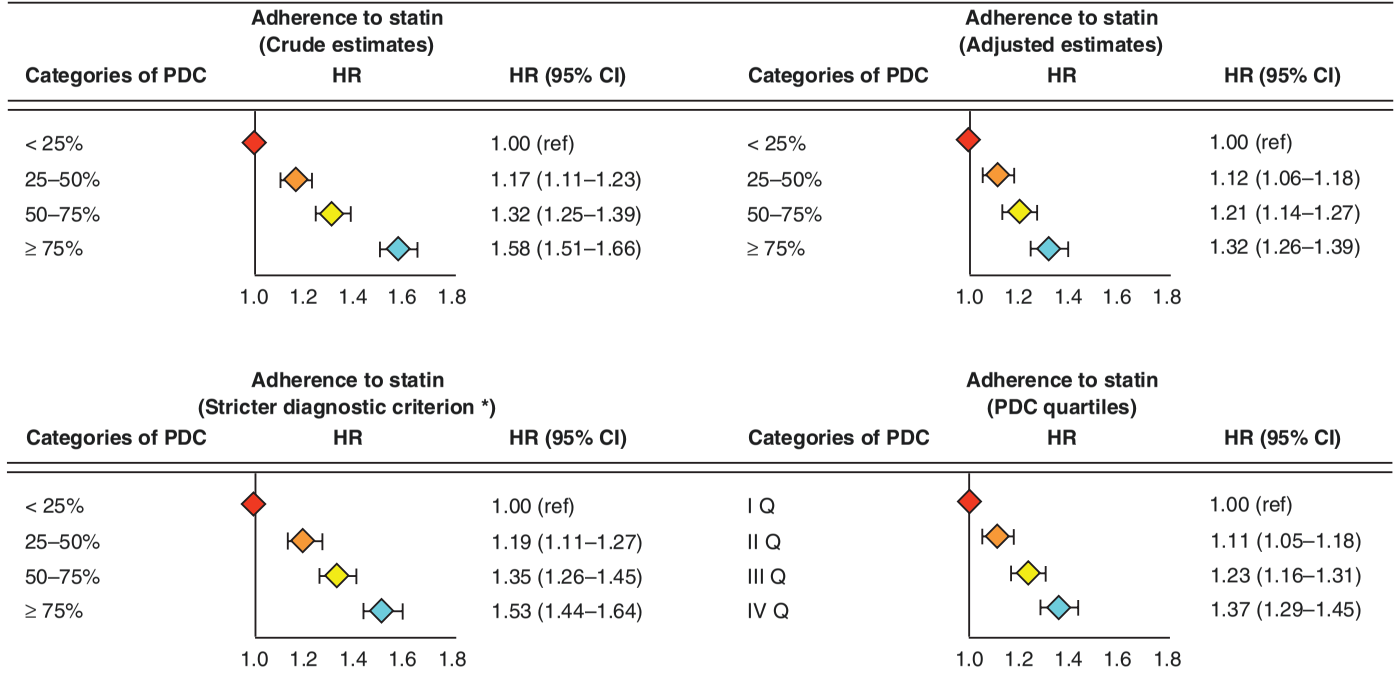


Fig. 5.9 Increased risk of new onset diabetes with different adherence to statin treatment as measured by the ratio between time covered by statin prescription and total follow-up time. The overall number of patients was 115,709 and the follow-up 1 year or longer. Data are shown by taking into account several possible confounders. Note that when analysis was performed by a more specific identification of new onset diabetes (three consecutive new prescriptions of antidiabetic drugs) patients maximally adherent to statin showed a 53% increase. *Q* quartile. Reference (ref): adherence of <25% of the follow-up time (From [29], with permission)

References

1. Haynes RB McDonald H, Garg AX, Montague P. Interventions for helping patients to follow prescriptions for medications. Cochrane Database Syst Rev. 2002;(2):CD000011.
2. Goodwin MA, Stange KC, Zyzanski SJ, Crabtree BF, Borawski EA, Flocke SA. The Hawthorne effect in direct observation research with physicians and patients. J Eval Clin Pract. 2017;23(6):1322–8. https://doi.org/10.1111/jep.12781.
3. Chowdhury R, Khan H, Heydon E, Shroufi A, Fahimi S, Moore C, Stricker B, Mendis S, Hofman A, Mant J, Franco OH. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. Eur Heart J. 2013;34(38):2940–8.
4. Corrao G, Mancia G. Generating evidence from computerized healthcare utilization databases. Hypertension. 2015;65(3):490–8.
5. Corrao G, Zambon A, Parodi A, Poluzzi E, Baldi I, Merlino L, Cesana G, Mancia G. Discontinuation of and changes in drug therapy for hypertension among newly-treated patients: a population-based study in Italy. J Hypertens. 2008;26(4):819–24.
6. Corrao G, Parodi A, Nicotra F, Zambon A, Merlino L, Cesana G, Mancia G. Better compliance to antihypertensive medications reduces cardiovascular risk. J Hypertens. 2011;29:610–8.
7. Corrao G, Rea F, Ghirardi A, Soranna D, Merlino L, Mancia G. Adherence with antihypertensive drug therapy and the risk of heart failure in clinical practice. Hypertension. 2015;66:742–9.
8. Corrao G, Rea F, Monzio Compagnoni M, Merlino L, Mancia G. Protective effects of antihypertensive treatment in patients aged 85 years or older. J Hypertens. 2017;35:1432–41.
9. Mancia G, Zambon A, Soranna D, Merlino L, Corrao G. Factors involved in the discontinuation of antihypertensive drug therapy: an analysis from real life data. J Hypertens. 2014;32(8):1708–15.
10. Heran BS, Wong MM, Heran IK, Wright JM. Blood pressure lowering efficacy of angiotensin converting enzyme (ACE) inhibitors for primary hypertension. Cochrane Database Syst Rev. 2008;(4):CD003823.
11. Heran BS, Wong MM, Heran IK, Wright JM. Blood pressure lowering efficacy of angiotensin receptor blockers for primary hypertension. Cochrane Database Syst Rev. 2008;(4):CD003822.
12. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment in hypertension: 9-Discontinuations for adverse events attributed to different classes of antihypertensive drugs: meta-analyses of randomized trials. J Hypertens. 2016;34:1921–32.
13. Mancia G, Parodi A, Merlino L, Corrao G. Heterogeneity in antihypertensive treatment discontinuation between drugs belonging to the same class. J Hypertens. 2011;29:1012–8.
14. Corrao G, Soranna D, Merlino L, Mancia G. Similarity between generic and brand-name antihypertensive drugs for primary prevention of cardiovascular disease: evidence from a large population-based study. Eur J Clin Investig. 2014;44:933–9.
15. Simpson SH, Eurich DT, Majumdar SR, Padwal RS, Tsuyuki RT, Varney J, Johnson JA. A meta-analysis of the association between adherence to drug therapy and mortality. BMJ. 2006;333(7557):15.
16. Hirakawa Y, Arima H, Webster R, Zoungas S, Li Q, Harrap S, Lisheng L, Hamet P, Mancia G, Poulter N, Neal B, Williams B, Rogers A, Woodward M, Chalmers J. Risks associated with permanent discontinuation of blood pressure-lowering medications in patients with type 2 diabetes. J Hypertens. 2016;34:781–7.
17. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. Med Care. 2005;43(6):521–30.
18. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, Stoyanovsky V, Antikainen RL, Nikitin Y, Anderson C, Belhani A, Forette F, Rajkumar C, Thijs L, Banya W, Bulpitt CJ, HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008;358:1887–98.
19. Corrao G, Parodi A, Zambon A, Heiman F, Filippi A, Cricelli C, Merlino L, Mancia G. Reduced discontinuation of antihypertensive treatment by two-drug combination as first step. Evidence from daily life practice. J Hypertens. 2010;28:1584–90.

20. Egan BM, Bandyopadhyay D, Shaftman SR, Wagner CS, Zhao Y, Yu-Isenberg KS. Initial monotherapy and combination therapy and hypertension control the first year. Hypertension. 2012;59:1124–31.
21. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F. The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). 2013 ESH/ESC guidelines for the management of arterial hypertension. J Hypertens. 2013;31:1281–357.
22. Corrao G, Nicotra F, Parodi A, Zambon A, Heiman F, Merlino L, Fortino I, Cesana G, Mancia G. Cardiovascular protection by initial and subsequent combination of antihypertensive drugs in daily life practice. Hypertension. 2011;58:566–72.
23. Gradman AH, Parisé H, Lefebvre P, Falvey H, Lafeuille MH, Duh MS. Initial combination therapy reduces the risk of cardiovascular events in hypertensive patients: a matched cohort study. Hypertension. 2013;61:309–18.
24. Corrao G, Nicotra F, Parodi A, Zambon A, Heiman F, Merlino L, Fortino I, Cesana G, Mancia G. Cardiovascular protection by initial and subsequent combination of antihypertensive drugs in daily life practice. Hypertension. 2011;58:566–72.
25. Corrao G, Conti V, Merlino L, Catapano AL, Mancia G. Results of a retrospective database analysis of adherence to statin therapy and risk of nonfatal ischemic heart disease in daily clinical practice in Italy. Clin Ther. 2010;32:300–10.
26. Corrao G, Soranna D, Arfè A, Casula M, Tragni E, Merlino L, Mancia G, Catapano AL. Are generic and brand-name statins clinically equivalent? Evidence from a real data-base. Eur J Intern Med. 2014;25:745–50.
27. Corrao G, Zambon A, Parodi A, Merlino L, Mancia G. Incidence of cardiovascular events in Italian patients with early discontinuations of antihypertensive, lipid-lowering, and antidiabetic treatments. Am J Hypertens. 2012;25:549–55.
28. Corrao G, Ibrahim B, Nicotra F, Zambon A, Merlino L, Pasini TS, Catapano AL, Mancia G. Long-term use of statins reduces the risk of hospitalization for dementia. Atherosclerosis. 2013;230:171–6.
29. Corrao G, Ibrahim B, Nicotra F, Soranna D, Merlino L, Catapano AL, Tragni E, Casula M, Grassi G, Mancia G. Statins and the risk of diabetes: evidence from a large population-based cohort study. Diabetes Care. 2014;37:2225–32.

Directly Observed Therapy in Hypertension (DOT-HTN)

6

Ulla Hjørnholm, Mikaela Aamodt, Anne Cecilie Larstorp, Fadl Elmula M. Fadl Elmula, Aud Høieggen, Marit Helen Andersen, and Sverre E. Kjeldsen

6.1 Background and Rationale

DOT-HTN is a health personnel observed, or witnessed intake, of difficult-to-control hypertensive patients' medication before 24-hour ambulatory blood pressure measurement (24 h ABPM) and is a method introduced in hypertension research

U. Hjørnholm
Section of Cardiovascular and Renal Research, Oslo University Hospital, Ullevaal, Oslo, Norway
e-mail: ullhjo@ous-hf.no

M. Aamodt
University of Oslo Library, University of Oslo, Oslo, Norway
e-mail: mikaela.aamodt@ub.uio.no

A. C. Larstorp
Section of Cardiovascular and Renal Research, Oslo University Hospital, Ullevaal, Oslo, Norway

Department of Medical Biochemistry, Oslo University Hospital, Ullevaal, Oslo, Norway
e-mail: uxneld@ous-hf.no

F. E. M. Fadl Elmula
Section of Cardiovascular and Renal Research, Oslo University Hospital, Ullevaal, Oslo, Norway

Department of Acute Medicine, Oslo University Hospital, Ullevaal, Oslo, Norway

Department of Cardiology, Oslo University Hospital, Ullevaal, Oslo, Norway
e-mail: uxfafa@ous-hf.no

A. Høieggen
Section of Cardiovascular and Renal Research, Oslo University Hospital, Ullevaal, Oslo, Norway

Department of Nephrology, Oslo University Hospital, Ullevaal, Oslo, Norway

Institute for Clinical Medicine, University of Oslo, Oslo, Norway
e-mail: aud.hoieggen@medisin.uio.no

M. Burnier (ed.), *Drug Adherence in Hypertension and Cardiovascular Protection*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-76593-8_6

M. H. Andersen
Institute of Health and Society, University of Oslo, Oslo, Norway
e-mail: m.h.andersen@medisin.uio.no

S. E. Kjeldsen (✉)
Section of Cardiovascular and Renal Research, Oslo University Hospital, Ullevaal, Oslo, Norway

Department of Cardiology, Oslo University Hospital, Ullevaal, Oslo, Norway

Institute for Clinical Medicine, University of Oslo, Oslo, Norway
e-mail: s.e.kjeldsen@medisin.uio.no

during recent years. Our institution [1] has participated in, and followed the introduction of this method. We have observed and reported on the method in two hypertension studies [2, 3], and found only a few reports in the literature addressing the issue [4, 5]. Directly Observed Therapy, as an adherence assessment method, has been mentioned as part of the design considerations for future clinical trials in HTN [6], and is of particular interest to researchers involved with treatment resistant hypertension (TRH). Patients with TRH have a sustained systolic BP >140 mmHg and/or diastolic BP >90 mmHg despite a minimum of three different antihypertensive drug classes in highest tolerated doses including a diuretic during at least 6 months of treatment [7]. Another objective way of measuring adherence in TRH patients has been reintroduced almost simultaneously to DOT-HTN: By taking a blood- or urine sample and analysing it with e.g. high performance liquid chromatography coupled with mass spectrometry (HPLC-MS/MS), one can detect medication or its metabolites, at that particular point of time, if medication has been taken, given that the patient has a normal drug metabolism [8].

Prevalence of TRH is highly debated and range from 1 to 30% of the hypertension population [7]. Studies published during recent years question whether patients are true treatment resistant or rather non-adherent to medication [3, 4]. Ceral et al. [9] evaluated serum from 84 difficult-to-control hypertensive patients with HPLC-MS/MS and found components of *all* antihypertensive drugs in only 29 (34.5%) patients, and *no* detectable drugs in the serum of other 29 (34.5%) patients. Jung et al. [10] identified 76 (20%) TRH patients out of 375 uncontrolled hypertensive patients and assessed adherence to antihypertensive medications with urine screening. 40 of 76 (53%) patients were non-adherent to prescribed antihypertensive medications of which 12 patients had no detectable drugs in urine, 28 patients had incomplete adherence, and 24 of these had taken less than 50% of the prescribed drugs. Other studies confirm that objective evaluation of serum or urine reduces the number of patients with true TRH [11, 12].

Our group acquired first-hand experiences of how the procedure could lead to extraordinary situations when applied to hypertensive patients. Two of our cases are

described here to provide insight to real-life implementation of DOT-HTN and generate questions that in our view need to be addressed in the process of implementing DOT.

Case 1 *A young woman was referred from a specialist, with the specific wish to undergo renal denervation. She had children of younger age and expressed deep concern about the severe nature of her hypertension with end-organ damage. Her systolic BP was habitually around and above 200 mmHg. She said that she took her medications as prescribed, but with subsequent dizziness and nausea. In the referral letter it was specifically stated that there was no suspicion of non-adherence. She said that she had tried a variety of medications but none had lowered her BP satisfactory.*

The patient was screened according to procedure, which implicated DOT-HTN prior to ABPM. 15 to 20 min later she experienced extreme hypotension [13] *and was admitted to the Emergency Department.*

In a situation like this, it is important to question the safety of DOT-HTN. Are there any rare conditions or hypertension phenotypes that if recognized could have foreseen the acute development in this case? Can or should DOT-HTN be applied to anyone?

Case 2 *A much less dramatic, yet interesting case from another study concerned a middle-aged well-educated man whom in a letter was informed of DOT-HTN prior to the visit. The instructions were to bring his antihypertensive medications in original packaging, and not in a pre-dispensed pill-box. He was also informed that the medication should be taken in front of an investigator.*

Arriving to the visit he questioned the reason for using Directly Observed Therapy in general terms. He allegedly accepted the explanation given, that the procedure was used in the given study but was not in details informed of initially in the Informed Consent Form, otherwise jeopardizing the element of control. The investigator got up to fetch a glass of water facing away from the patient. When turning around again the patient said that he had swallowed the medication, without the investigator witnessing the intake.

This patient clearly did not want to take any medication under observation. He deliberately deviated from instructions given, but was not at any time confronted with his choice of behaviour. Would prior detailed information about DOT-HTN, have made him decline participation? Of note, the Informed Consent Form approved by the Ethics Committee stated that patients in one of the two groups in the study would have closer monitoring of treatment than that of the other group. These and other extraordinary cases in addition to reports from the literature [14] inspired us to conduct a review in order to elaborate more on DOT-HTN.

6.1.1 Historical Background of Directly Observed Therapy (DOT)

We begin with a short version of the inescapable historical background and the work of Dr. Karel Styblo [15] resulting in a global implementation of DOT. Directly observed therapy—short course (DOTS) was in 1994 endorsed by the World Health Organization [16] to fight the deadly and contagious disease tuberculosis. DOTS was a strategy to improve tuberculosis treatment adherence and outcome, and had five components: government commitment, quality laboratory facilities to assure diagnosis, continuous supply of high-quality drugs, management and documentation of progress and treatment effect on an individual level (monitoring, recording and reporting), and direct observation by health personnel of patients taking their medication [15, 17]. By 2008 the implementation of DOTS in more than 190 countries had cured 36 of 43 million patients [18]. DOTS furnished countries of poor health infrastructure with a long awaited framework enabling the health authorities to manage and treat a deadly contagious disease. DOTS has since been criticized both in regard to its effect on adherence and outcome [19, 20], and the ethical aspect of the legislation forced on people. In Norway, all asylum-seeking refugees are screened according to the DOTS framework incorporated in the law [21], and treated if disease is detected. Tuberculosis medications are highly toxic, with possible severe adverse effects on the liver and the eyes that can lead to death or blindness. The close monitoring of medication intake and adverse reactions in patients are therefore crucial functions of the DOTS framework [19].

A few years after DOTS was globally implemented an initiative was launched to do the same in the treatment of human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) [22]. The similarities of the two diseases in terms of uncontrolled global spread and need for uninterrupted high-quality drug supplies as well as monitoring and reporting are obvious, and the term directly observed therapy with antiretroviral therapy (DOT-ART) has since labeled the procedure and enabled researchers and stakeholders to separate it from DOTS. The most visible difference between DOTS and DOT-ART is the lifelong treatment profile of HIV/AIDS, in comparison to the "short course" profile of tuberculosis [15].

6.1.2 DOT in Hypertension

The use of DOT in hypertension is rather new. We introduce the concept DOT-HTN, to separate it from DOTS and DOT-ART, and to make it easier searchable for researchers interested in the concept. Studies have reported the use of DOT-HTN prior to 24 h ABPM since 2011 [2–4, 13, 23]. In 2016, Hameed et al. [5] reported having established a "DOT clinic" in 2007 at the Birmingham Heartlands Hospital, UK, headed by a clinical pharmacist and run by a specialist hypertension nurse. Other such initiatives might exist [4] but are to our knowledge not reported in the literature.

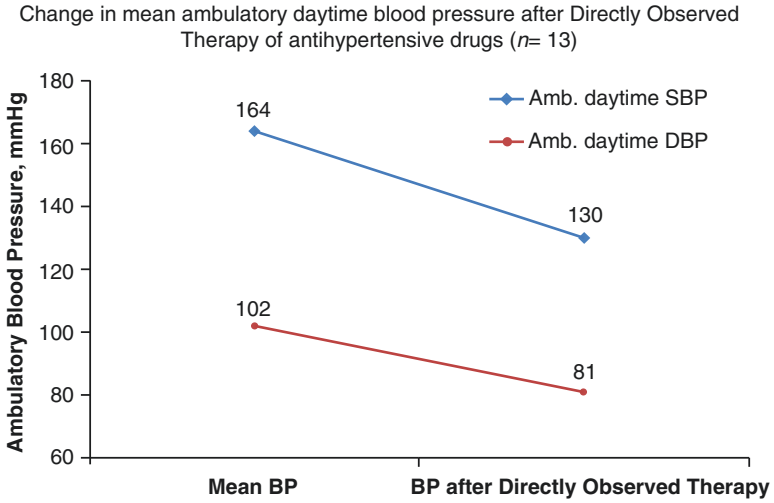


Fig. 6.1 In the Oslo RDN Study [3] $n = 13$ patients were confirmed non-adherent to their antihypertensive medication after DOT-HTN prior to ABPM (previously unpublished, the figure shows that in these 13 patients who were identified as non-adherent the mean ambulatory daytime blood pressure (BP) fell from 164 to 130 mmHg systolic and from 102 to 81 mmHg diastolic)

A one-time adherence control with DOT-HTN prior to ABPM will after only 24 h give you the results of the patients true BP-lowering effect of the prescribed regimen—in writing. DOT-HTN provides an objective measurement tool that exempts physicians from relying on their own (poor) judgement of the patient's adherence [24] or the patient's own (unreliable) declaration of adherence [25, 26].

We were among the first to introduce DOT in hypertensive patients (Fig. 6.1), as a screening tool in studies regarding renal denervation (RDN) in treatment resistant hypertensive patients [2, 3]. Contemporary randomized controlled RDN trials conducted between 2010 and 2015 [13] did not use DOT as direct assessment method of treatment adherence, instead they used serum drug concentration [27, 28], one of these in combination with a questionnaire [28], or indirect assessment methods like diaries [29–31] and interviews [32].

6.1.2.1 Safety of DOT in Hypertension

The safety profile of DOT-HTN has been reported to vary from drug-induced adverse effects such as light hypotension [5] to severe hypotension [3, 5] leading to renal failure [14]. One element of importance to safety is that health personnel do not administer medications from pre-dispensed pill-boxes brought by the patient, but dispense from original packaging brought by the patient, alternatively prescribed from the hospital pharmacy [5] (Fig. 6.2).

Fig. 6.2 How to dispense drugs: One element of importance to safety is that health personnel do not administer medications from pre-dispensed pill-boxes, but dispense from original packaging

6.2 Methods

We used the PRISMA 2009 checklist [33], as a tool to build the review, though not the entire 27 items, since we did not conduct a meta-analysis, and did not have any focus on effect, i.e. DOT's effect on BP.

Besides PRISMA, we used the definitions in Grant and Booth's 2009 [34] review article: *A typology of reviews: an analysis of 14 review types and associated methodologies.* Grant and Booth describe the differences and similarities between the various kinds of reviews, and how to best fit the right review methodology to the question it is meant to address [34]. In the discussion, we provide ethical considerations regarding DOT-HTN, based on a comparison of one of the case reports identified in the literature, and our case # 1, followed by suggestions of ethical considerations prior to future research on DOT-HTN.

6.2.1 Research Questions

The questions we wanted to find answers to were:

1. What has been published on DOT-HTN so far, that can inform us of the geographical spread of DOT-HTN, and on which level of care the procedure is applied, and what kind of research on DOT-HTN is ongoing?
2. Do DOT-HTN procedures exist, that could form a future safe standard research procedure?

6.2.2 Review Methodologies and Literature Search

In Grant and Booth's [34] review, there are 7 of 14 review methodologies which in their own ways could be used to answer our questions, confirming that there are no "one size fits all" approach to a review process [34]. The review methodologies that

in their different ways are fit for purpose in the current review are the literature review, the mapping review, the overview, the rapid review/rapid evidence assessment, the scoping review, the systematic search and review, and the systematized review [34].

Based on the research questions, we decided to do a systematized review (SyR) [34]. In a SyR, one attempts to do a systematic review without the comprehensiveness fundamental to a systematic review. The SyR methodology requires a systematic literature search and a subsequent cataloguing of citations.

A systematic search was performed in Ovid MEDLINE, PubMed, The Cochrane Library, and EMBASE for citations through March 31st 2016, using both MeSH terms and free text terms relating to Directly Observed Therapy in patients with hypertension.

6.2.3 Selection Criteria

We aimed to include all studies in English on DOT in hypertension regardless of date of publication, scientific quality and type of report, with the exception of abstracts and short commentaries. Citations from the field of tuberculosis and HIV/AIDS were considered as non-eligible. Grey literature (e.g. internal web-based standard operational procedures) was not part of the search. Due to DOT-HTN being a novel procedure, the selection criteria were deliberately broad to capture all types of reported attempts to use DOT-HTN. We would add citations found by hand searching bibliographies in relevant papers, and corresponded with colleagues to identify missed citations. Eligible citations were exported to our EndNote Library and checked for duplicates.

6.2.4 Search in International Trials Registries

To identify the present use of DOT-HTN in research an advanced search in International Committee of Medical Journal Editors (ICMJE) [35] endorsed primary registries of WHO International Clinical Trials Registry Platform (ICTRP) [36] was conducted using the terms: directly observed therapy, witnessed intake of medication and hypertension.

In summary, four literature databases [37–40] and 12 trial registries [41–53], were searched in the effort to map what have come out of already conducted research on DOT-HTN and what research is ongoing.

6.2.5 Data Extraction from Published Research

Extracted data from the published material included year of publication, research location, type of report, method/design, participant characteristics, number of antihypertensive drugs, pre- and post-DOT-HTN blood pressure measurements.

DOT-HTN procedure: To describe the procedure, the following ten key points of information were extracted: Level of care, group of patients, anamnestic- and investigational procedures prior to DOT, information given to patients prior to DOT, time of DOT, administration of medications, medical observations immediately after DOT, safety measurements, information given to patients after DOT, and follow-up visits.

Ongoing research: Extracted data from the ongoing research were trial registry, unique study ID-number, location of study, commercial status, study title, main objective, primary endpoint, planned number of subjects to be included, and the role of DOT-HTN.

6.3 Results

6.3.1 Identified Ongoing Trials

Search in trial registries identified three [2, 3, 54] of the five published trials and five ongoing trials. In summary, two trials [55, 56] were pharmaceutical RCTs, where DOT was part of the screening of eligibility before enrolment, planning to enrol 40 and 30 participants, respectively. One study [56] described the DOT-procedure used. The remaining three trials were designed as retrospective interventional [57], RCT (pilot) [58], and prospective observational [59], planning to enrol 100, 20, and 60 participants, respectively. Two studies [58, 59] described the DOT-procedure used.

6.3.2 Identified Published Research

The literature search identified ten publications (Fig. 6.3). Among the ten citations reviewed, three came from Norway, the others from the United Kingdom, Germany, and Canada. Half of the citations were studies [2–4, 54], the remainder consisted of two reviews [60, 61], two case reports [14, 62], and one editorial [63] (Table 6.1). All citations referred to DOT-HTN of treatment resistant hypertensive patients. One study [4] used DOT-HTN to identity non-adherence in uncontrolled hypertensive patients. Three studies [2, 3, 54] and one case report [14] used DOT-HTN as a screening tool to verify resistance to hypertensive medications prior to RDN. One patient in the other case report [62] had already had the renal denervation procedure done before adherence assessment with DOT-HTN. One study [5] reported on patients who were worked-up following a standard protocol mainly prior to RDN. In total 68 patients were reported non-adherent after DOT-HTN in seven citations.

In eight [2–5, 14, 54, 60, 62] of ten citations, the DOT-HTN procedure was described (Table 6.2). Ten key points of information were identified in the eight reports that described DOT-HTN procedures. Three reports, all Norwegian, had

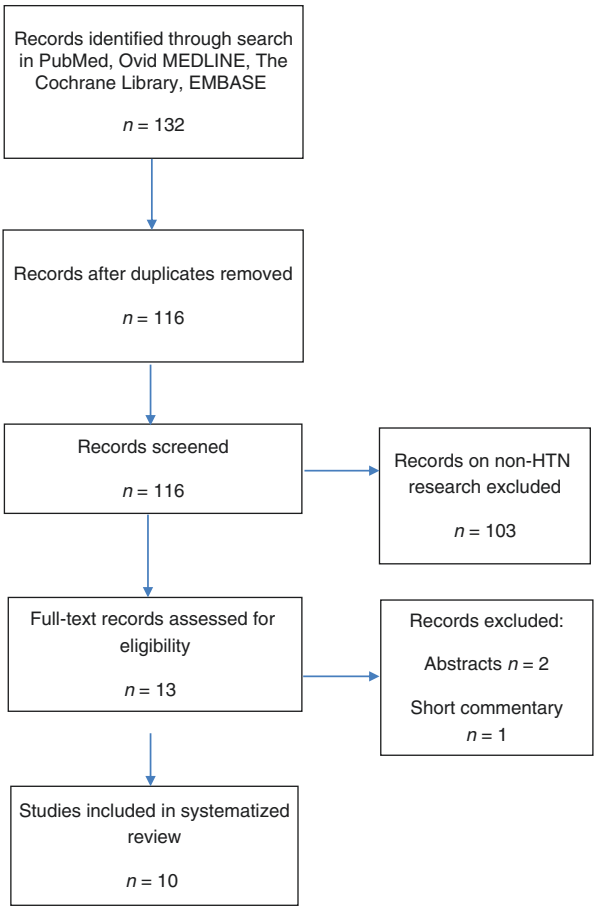


Fig. 6.3 PRISMA [33] flowsheet, showing the record selection process

rather similar procedures with a maximum of 2 h of post-DOT-HTN observation. The two case reports, described severe post-DOT-HTN adverse reactions. Three reports had longer observation time, two of them with medication administration intervals, instead of complete morning dose administration. All reports either described safety measures or discussed the safety of the procedure. In eight of ten publications, no characteristics of the patients were described. The two case reports [14, 62] provided detailed information about their cases including age, gender, and number of antihypertensive medications which includes diuretics. The five studies provided no demographic information about the non-adherent patients.

Three studies [3–5] reported pre- and post-DOT-HTN blood pressure measurements, one of them [3] ABP, two of them [4, 5] OBP and ABP. One study [54] provided no data on the two non-adherent patients.

Table 6.1 Differences in the reporting of patient characteristics after directly observed therapy in hypertension

NCT no.	–	NCT01673516	NA	NCT01673516	NA
Year of report (reference)	2011 [4]	2013 [2]	2013 [60]	2014 [3]	2014 [61]
Location	London, UK	Oslo, Norway	Ottawa, Canada	Oslo, Norway	Cambridge, UK
Type of report	Research letter	Original article	Case report	Original article	Editorial
Method/design	Prospective observational	Prospective observational	Case report	Randomized controlled trial	–
Patients with applied DOT-HTN (% women)	*n* = 37 (64.8%)	*n* = 18 (11%)	*n* = 1 (100%)	*n* = 65 (–)	–
Age, all patients, years, mean (range)	57 (20–87)	(39–68)	53	–	–
Patients confirmed true treatment resistant after DOT-HTN	*n* = 14	*n* = 6	*n* = 0	*n* = 19	–
Patient considered non-adherent after DOT-HTN (%)	***n* = 23 (62.2%)**	***n* = 3 (16.6%)**	***n* = 1 (100%)**	***n* = 13 (20%)**	–
Age, years	–	–	53	–	–
Gender (% male)	–	–	Female	–	–
No. of antihypertensive drugs	–	–	6	–	–
On diuretics (%)	–	–	1 (100%)	–	–
OSBP in mmHg at referral or baseline, mean	179	–	177	–	–
ODBP in mmHg at referral or baseline, mean	98	–	106	–	–
OSBP in mmHg after applied DOT-HTN, mean	144	–	97 (after 1 h) 94 (after 2 h) 140 (after 6 h)	–	
ODBP in mmHg after applied DOT-HTN, mean	83	–	68 (after 1 h) 68 (after 2 h) 75 (after 6 h)	–	–
Decrease in OSBP in mmHg pre- to post-DOT-HTN	–	–	–	–	–

Table 6.1 (continued)

NCT no.	–	NCT01673516	NA	NCT01673516	NA
Year of report (reference)	2011 [4]	2013 [2]	2013 [60]	2014 [3]	2014 [61]
Decrease in ODBP in mmHg pre-to post-DOT-HTN	–	–	–	–	–
ASBP in mmHg at referral or baseline, mean (±SD)	–	–	176 (after 5 h)	24 h 160 (20)	–
ADBP in mmHg at referral or baseline, mean (±SD)	–	–	100 (after 5 h)	24 h 99 (16)	–
ASBP in mmHg after applied DOT-HTN, median (range) or mean (±SD)	dt 139 (111, 207)	[a]	dt 135	24 h 130 (5)	–
ADBP in mmHg after applied DOT-HTN, median (range) or mean (±SD)	dt 80 (63, 97)	[a]	dt 69	24 h 81 (5)	–
Decrease in ASBP in mmHg pre-to post-DOT-HTN	–	–	–	–	–
Decrease in ADBP in mmHg pre- to post-DOT-HTN	–	–	–	–	–
DOT-HTN procedure described	Yes	Yes	Yes	Yes	–
Health personnel applying DOT-HTN	Specialist nurse	Physician	–	Physician/nurse	–
Defined cut-off value to indicate non-adherence	–	–	–	–	–
Safety reported/ discussed	Yes	Yes	Yes	Yes	Yes

(Table 6.1 continued) NCT no.	NA	_	NCT 01630928	NA	NA
Year of report (reference)	2014 [14]	2015 [5]	2015 [52]	2015 [58]	2015 [59]
Location	Homburg/ Saar, Germany	Birmingham, UK	Tromsø, Norway	Ottawa, Canada	Oslo, Norway
Type of report	Letter to the editor	Original article	Original article	Review	Review
Method/design	Case report	Retrospective observational	Prospective observational	Review	Review
Patients with applied DOT-HTN (% women)	$n = 1$ (0%)	$n = 50/48$[b] (52.1%)	$n = 25/23$[b] (21%)	–	–

(continued)

Table 6.1 (continued)

(Table 6.1 continued) NCT no.	NA	_	NCT 01630928	NA	NA
Year of report (reference)	2014 [14]	2015 [5]	2015 [52]	2015 [58]	2015 [59]
Age, all patients, years, mean (range) or (±SD)	59	(*n* = 48) 62.0 (11.0)	(*n* = 23) 53 (8.4)	–	–
Patients confirmed true treatment resistant after DOT-HTN	*n* = 0	*n* = 25	*n* = 23	–	–
Patient considered non-adherent after DOT-HTN (%)	***n* = 1 (100%)**	***n* = 25 (50%)**	***n* = 2 (8%)**	–	–
Age, years	59	–	–	–	–
Gender (% male)	Male	–	–	–	–
No. of antihypertensive drugs	10	–	–	–	–
On diuretics (%)	1 (100%)	–	–	–	–
OSBP in mmHg at referral or baseline, mean (±SD)	–	184.1 (23.9)	–	–	–
ODBP in mmHg at referral or baseline, mean (±SD)	–	102.5 (21.4)	–	–	–
OSBP in mmHg after applied DOT-HTN	70	–	–	–	–
ODBP in mmHg after applied DOT-HTN	50	–	–	–	–
Decrease in OSBP in mmHg pre- to post-DOT-HTN	–	–	–	–	–
Decrease in ODBP in mmHg pre- to post-DOT-HTN	–	–	–	–	–
ASBP in mmHg at referral or baseline, daytime/nighttime mean	168/169	[a]	–	–	–
ADBP in mmHg at referral or baseline, daytime/nighttime mean	108/114	[a]	–	–	–
ASBP in mmHg after applied DOT-HTN, daytime/nighttime mean	97/90	[a]	–	–	–
ADBP in mmHg after applied DOT-HTN, daytime/nighttime mean	60/54	[a]	–	–	–
Decrease in ASBP in mmHg pre- to post-DOT-HTN, mean(±SD)		24 h 19.5 (10.7) dt 18.4 (11.3) nt 20.6 (18.1)	–	–	–
Decrease in ADBP in mmHg pre- to post-DOT-HTN, mean(±SD)		24 h 9.4 (8.2) dt 8.4 (8.3) nt 11.4 (10.9)	–	–	–
DOT-HTN procedure described	Yes	Yes	Yes	Yes	Yes

Table 6.1 (continued)

(Table 6.1 continued) NCT no.	NA	_	NCT 01630928	NA	NA
Year of report (reference)	2014 [14]	2015 [5]	2015 [52]	2015 [58]	2015 [59]
Health personnel applying DOT-HTN	Physician	Hypertension nurse	Physician	–	–
Defined cut-off value to indicate non-adherence	–	>5 mmHg	–	–	–
Safety reported	Yes	Yes	Yes	Yes	Yes

NCT no. ClinTrial.gov identification, – not reported, *NA* not applicable, *RCT* randomized controlled trial, *DOT-HTN* directly observed therapy in hypertensive patients, *OBP* office systolic blood pressure, *ODBP* O diastolic BP, *ASBP* ambulatory SBP, *OSBP* office systolic blood pressure, *h* hour(s), *24 h* 24 hour, *dt* daytime, *nt* nighttime

[a]Reported in figures not numbers

[b]Total *n*/*n* with reported gender

6.3.3 DOT-HTN Procedures Reported in the Reviewed Literature

To emphasize what was published on the DOT-HTN procedure, we chose in this section to provide a narrative summary of all critical information clearly stating the procedures used, beginning with the earliest identified report from 2011, followed by tabulated key points in Table 6.2.

Bunker et al. 2011 [4]: "How common is true hypertension?"

Bunker et al. reported from a specialist nurse-led clinic where drugs were administered under observation ideally combined with a subsequent ABPM. Patients should meet medication fasting between 9 and 10 am. BP was recorded with a validated automated monitor using a standardized technique, immediately followed by oral drug administration. BP was then measured in intervals of 10–15 min for 2–4 h. *"In patients on three or more drugs the initial administration consisted of giving two of their prescribed drugs (usually a calcium channel blocker and an angiotensin converting enzyme inhibitor or angiotensin receptor blocker) with the additional drugs (diuretics, β-blockers, α-blockers, etc.) administered at appropriate intervals over the ensuring 2–4 hours, depending on blood pressure responses"* [4]. Due to an adverse response with severe hypotension after administration of the α-blocker doxazosin they *"…proposed that for patients prescribed higher doses of doxazosin, a maximum dose of 4 mg…should be administered in the context of the tablet feed"* [4].

Fadl Elmula et al. 2013 [2]: "Renal sympathetic denervation in patients with treatment-resistant hypertension after witnessed intake of medication before qualifying ambulatory blood pressure"

"Patients were asked to bring their prescribed medication to the clinical visit… Medication was documented and administered by the investigator and swallowed by the patient under continuous observation, to secure the intake of prescribed medication, in prescribed doses. Patients were then continuously under the observation by the investigator to prohibit throwing up again of the pills until 24-hour

Table 6.2 Key points of information in published reports on the DOT-HTN procedure

Year of report (reference)	2011 [4]	2013 [2]	2013 [60]	2014 [3]	2014 [61]
Location	London, UK	Oslo, Norway	Ottawa, Canada	Oslo, Norway	Cambridge, UK
Type of report	Research letter	Original article	Case report	Original article	Editorial
Level of care	Specialist HTN centre	Nephrology HTN centre	Renal HTN clinic	Nephrology HTN centre	_
Group of patients	Uncontrolled hypertensives on ≥ 3 antihypertensive drugs	Treatment resistant hypertensives	Individual case	Treatment resistant hypertensives	_
Anamnestic and investigational procedures prior to DOT	Antihypertensive drug and dose adjustments, exclusion of secondary HTN, patient-confirmed drug adherence	CT, MRI, and BT verified normal renal function, type 1 diabetes and secondary HTN excluded, antihypertensive drugs and doses of stabil for 2 w, no preplanned changes for 6 m	Co-morbidity status, exclusion of end organ damage, filling records verified with patients pharmacy, ABPM, RDN. Casual and resting sitting BP	CT, MRI, and BT verified normal renal function, type 1 diabetes and secondary HTN excluded, antihypertensive drugs and doses of stabil for 2 w, no preplanned changes for 6 m	_
Information given to patient prior to DOT	Omission of morning antihypertensive drugs	Patients asked to bring prescribed antihypertensive drugs in original packaging	Patient asked to omit morning antihypertensive drugs	Patients asked to bring prescribed antihypertensive drugs in original packaging	_
Time of DOT	9–10:00 AM	Morning	8:00 AM	Morning	_
Administration of medication	BP recorded followed by oral adm of antihypertensive drugs. Patients with ≥3 drugs: 2 drugs adm first, the rest during 2–4 h	Physician documented and adm antihypertensive drugs and observed patient swallow pills	Morning antihypertensive drugs adm	Physician documented and adm antihypertensive drugs and observed patient swallow pills	_
Medical observations immediately after DOT	BP recorded at 10–15 min intervals for 2–4 h	Prolonged mounting and testing of ABPM device	Hourly BP monitoring	Mounting and testing of ABPM device, clinical examination	_

Safety measures	α-blocker doxazosin max 4 mg	2 h on the hospital premises	Follow-up 6 h, future recommendation: Follow-up 4 h	2 h on the hospital premises	_
Information given to patients after DOT	_	If normalized BP patient informed of non-eligibility to HTN-study	_	If normalized BP patient informed of non-eligibility to HTN-study	_
Follow-up visits	1–18 month	_	Yes	_	_

(Table 6.2 continued) Year of report (reference)	2014 [14]	2015 [5]	2015 [52]	2015 [58]	2016 [59]
Location	Homburg/Saar, Germany	Birmingham, UK	Tromsoe, Norway	Ottawa, Canada	Oslo, Norway
Type of report	Letter to the editor	Original article	Original article	Review	Review
Level of care	Internal Medical Department	Specialist HTN clinic/DOT clinic	Cardiology and nephrology specialist centre	Cardiology and nephrology specialist centre	Nephrology HTN centre
Group of patients	Individual case	Uncontrolled hypertensives	Treatment resistant hypertensives	Treatment resistant hypertensives	Treatment resistant hypertensives
Anamnestic and investigational procedures prior to DOT	Co-morbidity status, exclusion of secondary HTN, ABPM, RDN, TDM in serum/urine	Standard protocol: medical history, clinical examination, OBP, BT, ABPM, ECG, ECHO. Serum/urine hormone screening if suspected secondary HTN, renal CTA. Lifestyle modification advice, adjustment of antihypertensive drugs, drug use review, prescription refill frequency (verified with pharmacy)	Standard clinical evaluation, BT, exclusion of secondary HTN, ABPM	Indirect adherence assessment methods (i.e. pill count, refill records, phone or internet based reminders	_

(continued)

Table 6.2 (continued)

(Table 6.2 continued) Year of report (reference)	2014 [14]	2015 [5]	2015 [52]	2015 [58]	2016 [59]
Information given to patient prior to DOT	_	Patients adviced to omit antihypertensive drugs on the day of the DOT clinic	Patients asked to bring prescribed antihypertensive drugs in original packaging	_	_
Time of DOT	Morning	_	_	_	_
Administration of medication	During morning ward round the patient was asked to take his medication under supervision of the treating physician	Clinical pharmacist prescribed patient antihypertensive drugs on a chart. Nurse compared patients drugs with drug chart. If patients took branded drugs they were adm own drugs. Nurse adm 1 drug every 60 min	Antihypertensive drugs were documented and adm by nurse, and swallowed under observation	Morning dose of antihypertensive drugs observed taken by the patient	_
Medical observations immediately after DOT	2 h post-DOT-HTN patient reacted to antihypertensive drugs, subsequent kidney failure	All symptoms recorded	Patients under continous observation until 24 h ABPM device was mounted and tested	BP measurements until BP plateau achieved	_
Safety measures	_	Antihypertensive drugs adm with 60 min intervals, patients observed for 7 h	_	4–6 h post-DOT-HTN observation of the patient until BP plateau achieved	_
Information given to patients after DOT	_	_	_	_	_
Follow-up visits	_	_	_	_	_

NCT no. ClinTrial.gov identification, – not reported, *NA* not applicable, *DOT-HTN* directly observed therapy of hypertensive patients, *HTN* hypertension, *CT(A)* computed tomography *(angiography)*, *MRI* magnetic resonance imaging, *BT* blood test, *TDM* therapeutic drug monitoring, *OBP* office BP, *ABPM* ambulatory BP measurement, *ECG* electrocardiogram, *ECHO* echocardiography, *adm* administer, *h* hour, *w* week, *m* month, *BP* blood pressure

ambulatory BP device had been mounted and tested out in a somewhat more lengthy procedure than usually to prolong the period of observation. Patients stayed in the hospital for 2 hours to capture those with potential symptomatic hypotension caused by full intake of medication. Visits with subsequent ambulatory BP measurement were done in the morning, and further observation of patients in the hospital was done during working hours" [2].

Ruzicka et al. 2013 [62]: "Adherence to blood pressure-lowering drugs and resistant hypertension: should trial of direct observation therapy be part of pre-assessment for renal denervation?"

"To exclude pseudo-resistance from non-adherence, filling records for the patients antihypertensive medications were verified with her pharmacy…" The patient was asked *"…not to take her morning medication and present to the clinic at 8 AM, at which time she was seated in the office, and casual and resting sitting, as well as upright, BP were recorded…She was then given her usual morning antihypertensive medications. Subsequently, hourly BP monitoring…showed a dramatic reduction in BP"* [62].

Fadl Elmula et al. 2014 [3]: "Adjusted drug treatment is superior to renal sympathetic denervation in patients with true treatment-resistant hypertension".

"Patients were asked to bring their prescribed medication in original packaging to the clinical visit…Medication was documented and administered by the investigator and swallowed by the patient under continuous observation, in order to secure the intake of prescribed medication, in prescribed doses. Patients were then under the observation by the investigator in order to prohibit throwing up the pills until 24-hour ambulatory BP device had been mounted and tested and clinical examinations had been carried out. Patients stayed in the hospital for 2 hours in order to capture those with potential symptomatic hypotension caused by full intake of medication. Visits with subsequent ambulatory BP measurement were done in the morning, and further observation of patients in the hospital was done during daytime working hours" [3].

Brown 2014 [63]: "Resistant hypertension: resistance to treatment or resistance to taking treatment?"

Being an editorial, no procedures were described. Nevertheless, Brown writes that: *"An increasingly common clinical practice is to undertake 'directly observed therapy' (DOT), and most hypertension specialists have anecdotes of patients who swear to compulsive tablet taking, but collapse on the ward floor when administered a fraction of their supposed regimen. DOT is not a trivial exercise, requiring staff, time and a bed for the collapsing patient"* [63].

Linicus et al. 2014 [14]: "Witnessed drug intake before planned denervation—Always harmless?"

Blood analyses detected only Carvedilol. *"During the morning ward round the patient was asked to take his medication under supervision of the treating physician. Two hours later he felt dizzy, light headed and suffered from nausea. Blood pressure reached levels of 70/50 mmHg…"* and he subsequently had indications of kidney failure. New blood analysis detected the presence of all drugs. After 2 days

with a new five-component medication regimen, he was normotensive without adverse drug effects [14].

Hameed et al. 2015 [5]: "Non-adherence to antihypertensive medication is very common among resistant hypertensives: results of a directly observed therapy clinic".

Hameed et al. followed a strict procedure in a special DOT clinic headed by a pharmacist and run by a specialist hypertension nurse. Patients were asked to meet medication fasting bringing their own medication. The pharmacist prescribed the patient's usual medication on a chart, which was then dispensed from the hospital pharmacy. The patient brought the medication to the DOT clinic where the hypertension nurse compared the patient's own medication to the pharmacy-dispensed medication. *"If patients were taking any branded medications, they were given their dose of the branded medication from their own supply instead of the generic medication supplied by the hospital pharmacy"* [5]. ABPM device was mounted prior to any administration of drugs. *"Each prescribed drug was administered at its current dose by the nurse, under the guidance of the clinical pharmacist; the first drug 1 h after arrival and thereafter at 60-min intervals. Patients were directly observed by the nurse for 7 h and all symptoms were recorded"* [5].

An arbitrary cut-off value of ≥5 mmHg was used to indicate non-adherence to treatment [5].

Miroslawska et al. 2015 [54]: "Renal sympathetic denervation: effect on ambulatory blood pressure and blood pressure variability in patients with treatment resistant hypertension. The ReShape CV-risk study".

"Patients were asked to bring their prescribed medication in original package to the clinical visit with one of the study nurses. Medication was documented, administered by the nurse and swallowed by the patient under continuous observation, to secure intake of the medication in prescribed doses. Patients were then continuously under observation by the nurse until 24-h ABPM device had been mounted and tested" [54].

Ruzicka et al. 2015 [60]: "Can drugs work in patients who do not take them? the problem of non-adherence in resistant hypertension".

"In our tertiary care referral clinic, we observe the patient for 4–6 h after directly observed administration of prescribed morning dose of BP-lowering drugs until the BP response plateaus. At this point, the patient is discharged home with a 24-h ambulatory BP-monitoring device" [60].

Eskås et al. 2015 [61]: "Adherence to medication and drug monitoring in apparent treatment resistant hypertension".

Eskås et al. states that: *"DOT is used to ensure intake of medication before assessing the treatment effect. In the assessment of hypertensive patients, the method is based on the patient taking the prescribed medications from original packaging in the correct doses, while being observed by a physician or trained nurse, before ambulatory BP measurement. The patient is often observed for some time to prevent them from spitting out the medications or vomiting, and for safety reasons, as a non-adherent patient may experience severe hypotension when all the medications are taken at once"* [61].

6.4 Discussion

Methods: This is, to our knowledge, the first review conducted on DOT-HTN with emphasis on the DOT-HTN procedure. Conducting a systematized review of published literature on DOT-HTN has provided important knowledge of the use of DOT-HTN and how the procedure is applied differently. Interestingly, the review revealed a clear knowledge gap concerning the characteristics of post-DOT-HTN non-adherent patients. Even though the systematized review is not at all as comprehensive as the systematic review, the literature search is still systematic and reproducible [34]. The search in clinical trial registers of ongoing trials provided important supplementary information about the DOT-HTN procedure in terms of use and location [34].

Since DOT is a new tool in hypertension research, with only a few quite different types of publications with diversities in methods and design, this early-stage systematized review was a useful methodology [64]. With the narrative and categorizing nature of the review, shortcomings in the reporting of patient characteristics as well as important safety information were interesting extractions.

The systematized review methodology provided an informative narrative and tabular synthesis of what is known about DOT-HTN, and contributed to future focus on the knowledge gap. High-profile organizations, like The Cochrane Collaboration [65] and the Campbell Collaboration [66] now include a wide range of study designs in their reviews [34], signalling that other study designs than RCTs (exclusively reviewed years back [67]), can inform health personnel and other stakeholders in future health decisions, taking into consideration that the majority of the literature in the HTN field is from non-randomized and epidemiological studies [68].

There are some methodological limitations to the conducted review. No critical appraisal of the included studies was part of the systematized review. Maybe in studies where DOT was used as a screening tool, the word-limitations to most abstracts left out the mentioning of DOT in the abstract. A clear limitation to this narrative and categorizing systematized review is the low number of identified studies, five ongoing trials and seven published patient-involving reports, therefore caution must be taken in concluding from such limited evidence. This systematized review is a first step towards more solid research.

Results: This review identified five ongoing studies, five published studies, and five other citations regarding DOT-HTN. All published patient-involving reports and three out of five ongoing trials provided information about the DOT-HTN procedures used. None of the published studies provided information on patient characteristics, in terms of age, gender, number of antihypertensive medications or duration of treatment; only the two case reports provided such information. One of the published [4] studies and three of the ongoing studies [57–59] used the procedure as a post-enrolment adherence assessment method. Publications from these three ongoing studies are of great importance in terms of filling the information gap on the patients who are found to be non-adherent. The remaining studies, published and ongoing, used DOT-HTN as a screening tool in their inclusion criteria, except the one case report [62] where the procedure was used post-renal denervation.

Publications from the two last mentioned ongoing studies [55, 56] are probably not expected to contribute with data on patients with screening failure, due to normalization of blood pressure after DOT-HTN. However, using the procedure as an adherence assessment method in a pharmaceutical trial, thereby ensuring that enrolled patients actually have high blood pressure despite taking their medications strengthens the result of the trials, and protects them from confounding white coat adherence [5]. White coat adherence is, when patients take their medication only prior to visits to their doctor, but not in between visits.

DOT-HTN procedures: There were differences in the DOT-HTN procedures that were used. In the three Norwegian studies [2, 3, 54] where DOT-HTN was a screening tool prior to enrolment in RDN studies, the DOT-HTN procedures were almost identical. Patients were instructed to bring their medication in original packaging and were observed taking their morning dose of prescribed drugs followed by mounting of ABPM device. The Oslo-studies [2, 3] reported 2-h post-procedural observation time, the Tromsø-study did not report any post-procedural observation time. The Norwegian procedures were relatively time efficient and easy implementable. One severe adverse reaction of hypotension was reported [3]. The canadian procedure [60] entailed observing the patients' intake of morning dose of antihypertensive medications, and monitored the blood pressure until it plateaued. They recommended 4–6 h of post-procedural observation. In the Birmingham study [5], they informed patients to omit morning dose of antihypertensive medications on the day of the visit and used a pharmacist-supported comprehensive standard DOT-HTN protocol. Drugs were administered in intervals of one drug every 60 min, allowing a reduction in number of medications administered, given symptoms of hypotension. Interval blood pressure monitoring was conducted. They had a 7-h post-procedural observation time. This procedure was time and labour consuming compared to the Norwegian procedure. The London study [4] had a less comprehensive DOT-HTN protocol compared to that of Birmingham; however, they initialized the drug administration with a maximum of two drugs, while measuring the post-DOT-HTN blood pressure in intervals of 10–15 min. The rest of the drugs were administered during 2–4 h with continuous BP measuring in 10–15 min intervals. The two case reports gave examples of extreme cases where DOT-HTN was used. Ruzicka et al. described a 53-year-old female, treated with antihypertensive medications for 20 years, and at the time of report, was on *post-RDN* medical treatment with six different antihypertensive drugs. DOT-HTN in this case was a long awaited resolve of the patient's treatment resistant hypertension. She had undergone invasive procedures before DOT-HTN revealed her real problem of non-adherence. Linicus et al. described a 59-year-old male, diagnosed with severe hypertension for 4 years, awaiting the invasive RDN procedure, and at the time of report was on ten different antihypertensive drugs. In this case, the patient suffered a severe adverse reaction following a DOT-HTN of *ten* antihypertensive drugs including doxazosin, a rather potent α-blocker often administered in the evening. The number and type of drugs considered, this was an example of what not to do in the future, and contributes with important safety information regarding DOT-HTN. In summary, the reviewed reports revealed huge differences in how DOT-HTN procedures were

implemented, ranging from ten drugs at one time to one drug every 60 min, with implications to the patients involved. Ethical considerations are important here as well, and will be discussed later in this chapter.

Hypertensive patients with post-DOT-HTN non-adherence: The results of this review revealed the very limited, almost non-existing knowledge of the patients who have been proven non-adherent with DOT-HTN, in terms of age, gender, number of antihypertensive medications, treatment duration, and other background information. Looking exclusively at the ten identified published and ongoing studies, 60% used DOT-HTN to determine patients' eligibility to further participation, which for the published studies part might have led to less attention being paid to the reporting of demographics on the post-DOT non-adherent patients. Only the case reports, provided demographic information, which is more likely to be explained by a lack of reporting, rather than a lack of knowledge even though, as Douglas G. Altman writes—*"reading a paper we cannot assume things that are not stated"* [69]. In the absence of knowledge about these patients, it can be relevant to look at other patients with similarities to those of the DOT-HTN-patients.

What we know in general from the literature on adherence in hypertensive patients is that estimated 50% of patients stop taking their medications after 1 year of treatment [24, 70, 71]. We also know that the higher the number of antihypertensive drugs the more it affects adherence in a negative way [25]. One review [72] stated that reducing the number of pills taken, was the single most effective adherence promoter. In one review [73] of qualitative studies, medicinal side-effects were an important reason for patients to adjust or stop their antihypertensive medication intake. It was also found that complicated drug regimens, costs of drugs, older age, poor social support, cognitive problems, and depression were associated with non-adherence [73]. One qualitative study (n = 118) [74] found gender-specific differences in adherence, i.e. that older age in men promoted adherence to antihypertensive drugs, as well as less education and fewer side-effects. Women's adherence was associated with, i.e. more causal attribution to risk factors and mental balance and less personal control (e.g. greater respect for authority). For both genders, adherence was associated with a better understanding of their illness [74].

It is known that large intra-individual variability in factors influencing the patients non-adherence behaviour exist [75] and Lisa Rosenbaum's paper *"Beyond Belief—How People Feel about Taking Medications for Heart Disease"* [76] is a must-read, with an interesting view into the patients' perceptions of taking medications. Her last sentence states that *"I want to believe that if patients knew what I know, they would take their medicine. What I've learned is that if I felt what they feel, I'd understand why they don't"* [76].

Where is DOT-HTN used and why? All the 15 reviewed reports and ongoing trials originated from only four different nations, namely the United Kingdom (London, Cambridge, Birmingham, Exeter, and Edinburgh), Norway (Oslo and Tromsø), Canada (Ottawa), and Germany (Homburg/Saar). This could imply that DOT-HTN to date has gained limited international interest, or that in particular the researchers who initiated the use of DOT-HTN in research, have found it of interest to investigate the use of the procedure. The latter might be explained by the highly

visible impact the procedure has, in terms of quick, measurable and visible responses in patients who do not adhere to their medications. One could speculate that seeing patients with long histories of severe apparent resistant hypertension reach treatment target of <140/90 mmHg, or even collapse from hypotension after actually ingesting the drugs they have secretively omitted, awakens both astonishment and curiosity and drives the observer to find out more about *who* and *why*! An example could be the researchers from Ottawa, Canada, with Primary Investigator Marcel Ruzicka, who published a case report [62] in 2013, a review [60] in 2015 and are now recruiting to a prospective observational study [59] of 60 participants investigating a four-step DOT protocol, which have been implemented as part of the standard care in their Nephrology Department [59]. Our Norwegian research team also published a prospective observational study [2] in 2013, an RCT [3] in 2014, a review [61] in 2016 and are now recruiting to a pilot RCT [58] of 20 participants, investigating DOT based on a 2013 procedure [2]. Researchers engaged in hypertension are not the only researchers interested in how a modification of the original DOTS might help their patients. Within the fields of haemodialysis [77], diabetes [15, 78], chronic hepatitis C infection [79], anticoagulation [80], and major mental illness [81] DOT has been investigated.

Who qualifies to undergo DOT-HTN? Since the literature tells us almost nothing about the patients found non-adherent after DOT-HTN, it is impossible to say exactly which patients qualify for DOT-HTN. Patients with uncontrolled hypertension leaning towards severe apparent treatment resistant hypertension, and who declare adherence to antihypertensive medications, would obviously be good candidates. The apparent treatment resistant hypertensive patients represent inadequately treated patients, patients with white coat hypertension, patients with secondary causes of hypertension, and the patients who secretively omit their drugs and are non-adherent to treatment. The question is who and when health personnel should test adherence with DOT-HTN. If the patient claims to be adherent to the treatment regimen agreed on, and treatment has been adjusted in case of adverse reactions, the next step is often a costly investigation of secondary causes to HTN, in a hospital setting. Secondary investigations can be expensive and time and labour demanding, and include blood test screening for kidney function and hormones. It can include a sleep apnea test, or infusion of a chemical substance, a contrast, prior to computed tomography with angiography (CTA) or magnetic resonance imaging (MRI) of kidneys to look for stenosis in kidney arteries or adenomas in adrenal glands (or other kidney disease that could explain the high blood pressure) [7]. In the editorial by Morris J. Brown [63] he states that patients who do not willingly allow a test of adherence, e.g. by the use of DOT-HTN or blood screening to identify antihypertensive drugs, maybe should not gain the opportunity to be investigated for secondary causes with costly methods. Ethically this is problematic of course. Health personnel cannot force people to live healthy lives, or take prescribed medication, or follow advice, and when they fall ill or illness is suspected, we must investigate to find a cause. In a newly published paper [82] from our research group, we found that 30% of apparent treatment resistant hypertensive patients referred for renal denervation had secondary causes to hypertension, corresponding with findings in other

RDN studies [83]. The proportion of patients with poor post-DOT-HTN drug adherence was in our study 32% [82], which was lower than in the Birmingham [5] and London [4] studies with 50% and 60%, respectively. An explanation could be, that more patients (n = 83) were screened in our study compared to the Birmingham study (n = 50) [5] and the London study (n = 37) [4], in combination with differences in the selection of patients. It seemed that both in Birmingham and London, they had an eye out for the non-adherent patients, in contrast to our study, where the proportion of non-adherent patients came as a surprising secondary finding.

What we can try to do in this case is to explain to the patients why tools like DOT-HTN can be a first step before commencing costly investigations. If we present DOT-HTN to patients in positive wording and not as a control, which if they decline would lead to limitations in which investigations we can offer them, then maybe the important trust between health personnel and patient prevails. Given a positive and supporting attitude from health personnel towards the patient, a DOT-HTN resulting in a fall in blood pressure indicating poor adherence, might even strengthen that relationship, in terms of an understanding of what is really the problem, and a new fresh start. It is important that health personnel do not condemn the non-adherent patients since that might prevent future collaboration.

Where should DOT-HTN take place? Both in the Birmingham [5] and London [4] studies, results were reported from specialist pharmacist- or nurse-led clinics, using comprehensive DOT-HTN protocols with safety measures like interval drug administration and continuous blood pressure monitoring. Both the Norwegian, Canadian, German, and British researchers in the review, reported cases of severe hypotension, in some cases in connection with the α-blocker doxazosin in higher doses than 4 mg. This could suggest that even though the patient declares adherence, health personnel should not fully rely on such declaration [25, 26], and limit the use of DOT-HTN to hospital settings where adequate care can be attributed.

DOT-HTN strengths: The strength of DOT-HTN is that the therapeutic response of the antihypertensive medications is clarified within 24 h at the most. With precautions to number and types of drugs, and in a hospital setting DOT-HTN has the potential to be a useful tool.

DOT-HTN weaknesses: The procedure has in some patients resulted in severe hypotension, even with one reported case of kidney injury and is probably not safe to use outside a hospital setting. It has been reported to be a time and labour demanding procedure, but there is no present consensus on the DOT-HTN procedure in the literature. DOT-HTN do not measure adherence in a long term perspective, so called drug persistence. Treatment of hypertension is often lifelong and using DOT-HTN is like a snap shot of the patient's adherence.

In summary, the DOT-HTN procedure might be useful, but much more high-quality research is needed before we can say that DOT-HTN is ready for clinical practice.

Ethical considerations: Ethical considerations are a crucial part of all health service and especially when we ask patients to participate in research. The young woman described in the case at the beginning of this chapter was examined thoroughly due to the severity of her situation [3]. Her post-DOT-HTN collapse raised

many questions about what caused the situation and how to avoid it in the future. It was a possibility that she had mislead the investigator, but one should consider if she was capable of comprehending the possible consequences of an intake of antihypertensive drugs "unknown" to her body, given that she habitually omitted them.

This particular case of DOT-HTN have some similarities to the case report of the middle-aged women in Canada [62], who had a long history of hypertension, which led to renal denervation. Post-RDN her doctors suspected that she omitted her antihypertensive drugs and performed a DOT-HTN, resulting in a dramatic fall in her blood pressure from 177/106 mmHg to 97/68 1 h post-DOT increasing to 140/75 mmHg after 6 h.

Assuming that the two women did not tell the truth, it is important to understand why. We already know that self-declaration of adherence is a highly questionable adherence assessment method, and it would be ethically wrong not to investigate the reasons why patients with very high blood pressure choose to omit drugs and lie about it. A worst-case scenario could be life-threatening adverse reactions to antihypertensive medications, at locations, e.g. the general practitioners office, where necessary life-saving resources might not be present. When introducing a known method to a new population, valuable information can be gained from qualitative research, like that of Lisa Rosenbaum [76], granting us important insight to the patients' reasoning, in a way that could help health personnel understand how to communicate to severe hypertensive patients the importance of treatment.

An important ethical challenge regarding DOT-HTN in a research setting is that informing the patients about an upcoming control of their adherence obviously induces the risk that they start taking their medications [84]. Patients with poor adherence might even decline participation, and selection bias is a fact. Even if you randomize patients to DOT-HTN and control, the control group might improve their adherence as well, simply due to the attention brought to their treatment, known as the Hawthorn effect [85].

Future research: In research including DOT-HTN, the focus should be on safety, in terms of the DOT-HTN procedure it-self, and where it is applied. It is important that we acquire comprehensive background information on the patients who are found non-adherent after DOT-HTN including their perspective on antihypertensive treatment. Knowledge about the patient perspective can be of invaluable help to health personnel in the important follow-up of non-adherent patients. A simple way to measure a patient's experience of DOT-HTN is, i.e. to use a visual analogue scale where the patients quantify his or her experience of their observed intake of medications. To learn about the patient's reasoning, the researcher can use a qualitative- or mixed method approach [86]. In-depth interviews of DOT-HTN revealed non-adherent patients could be an interesting future project.

Conclusions: In summary, a known procedure of directly observed therapy has been introduced to a new population, and it is important that randomized controlled trials are conducted, to investigate whether the DOT-HTN procedure is safe, and have any effect on adherence to antihypertensive medications and blood pressure in uncontrolled or treatment resistant hypertensive patients. This review found that no consensus exists on how DOT-HTN is applied, and that no information about the

patients found non-adherent after DOT-HTN exists. It is only when we gain knowledge of who they are, and why they don't take their medications, that we can improve patient adherence. Knowledge about ongoing trials and the identification of research groups interested in DOT-HTN might lead to international collaboration and future research funding, enabling high-quality research.

References

1. Cardiovascular and Renal Research Group 2018 [16 Mar 2018]. http://www.med.uio.no/klinmed/english/research/groups/cardiovascular-andrenal/index.html.
2. Fadl Elmula FE, Hoffmann P, Fossum E, Brekke M, Gjonnaess E, Hjornholm U, et al. Renal sympathetic denervation in patients with treatment-resistant hypertension after witnessed intake of medication before qualifying ambulatory blood pressure. Hypertension. 2013;62(3):526–32.
3. Fadl Elmula FE, Hoffmann P, Larstorp AC, Fossum E, Brekke M, Kjeldsen SE, et al. Adjusted drug treatment is superior to renal sympathetic denervation in patients with true treatment-resistant hypertension. Hypertension. 2014;63(5):991–9.
4. Bunker J, Callister W, Chang CL, Sever PS. How common is true resistant hypertension? J Hum Hypertens. 2011;25(2):137–40.
5. Hameed MA, Tebbit L, Jacques N, Thomas M, Dasgupta I. Non-adherence to antihypertensive medication is very common among resistant hypertensives: results of a directly observed therapy clinic. J Hum Hypertens. 2016;30(2):83–9.
6. Zannad F, Stough WG, Mahfoud F, Bakris GL, Kjeldsen SE, Kieval RS, et al. Design considerations for clinical trials of autonomic modulation therapies targeting hypertension and heart failure. Hypertension. 2015;65(1):5–15.
7. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34(28):2159–219.
8. Chung O, Vongpatanasin W, Bonaventura K, Lotan Y, Sohns C, Haverkamp W, et al. Potential cost-effectiveness of therapeutic drug monitoring in patients with resistant hypertension. J Hypertens. 2014;32(12):2411–21.
9. Ceral J, Habrdova V, Vorisek V, Bima M, Pelouch R, Solar M. Difficult-to-control arterial hypertension or uncooperative patients? The assessment of serum antihypertensive drug levels to differentiate non-responsiveness from non-adherence to recommended therapy. Hypertens Res. 2011;34(1):87–90.
10. Jung O, Gechter JL, Wunder C, Paulke A, Bartel C, Geiger H, et al. Resistant hypertension? Assessment of adherence by toxicological urine analysis. J Hypertens. 2013;31(4):766–74.
11. Strauch B, Petrak O, Zelinka T, Rosa J, Somloova Z, Indra T, et al. Precise assessment of noncompliance with the antihypertensive therapy in patients with resistant hypertension using toxicological serum analysis. J Hypertens. 2013;31(12):2455–61.
12. Tomaszewski M, White C, Patel P, Masca N, Damani R, Hepworth J, et al. High rates of non-adherence to antihypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis. Heart. 2014;100(11):855–61.
13. Fadl Elmula FE, Jin Y, Yang WY, Thijs L, Lu YC, Larstorp AC, et al. Meta-analysis of randomized controlled trials of renal denervation in treatment-resistant hypertension. Blood Press. 2015;24(5):263–74.
14. Linicus Y, Kindermann I, Helfer AG, Meyer MR, Maurer HH, Mahfoud F, et al. Witnessed drug intake before planned denervation—always harmless? Int J Cardiol. 2015;179:125–6.
15. Allain TJ, van Oosterhout JJ, Douglas GP, Joukes S, Gadabu OJ, Darts C, et al. Applying lessons learnt from the 'DOTS' Tuberculosis Model to monitoring and evaluating persons with diabetes mellitus in Blantyre, Malawi. Trop Med Int Health. 2011;16(9):1077–84.

16. World Health Organization. WHO Tuberculosis Programme; Framework for effective tuberculosis control 1994 [Search performed 02 May 2016]. http://apps.who.int/iris/handle/10665/58717. Accessed 16 Mar 2018.
17. Pasipanodya JG, Gumbo T. A meta-analysis of self-administered versus directly observed therapy effect on microbiologic failure, relapse, and acquired drug resistance in tuberculosis patients. Clin Infect Dis. 2013;57(1):21–31. https://doi.org/10.1093/cid/cit167.
18. Lonnroth K, Castro KG, Chakaya JM, Chauhan LS, Floyd K, Glaziou P, et al. Tuberculosis control and elimination 2010–50: cure, care, and social development. Lancet. 2010;375(9728):1814–29.
19. Volmink J, Garner P. Directly observed therapy for treating tuberculosis http://onlinelibrary.wiley.com. Wiley; 2012. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003343.pub3/abstract.
20. Ryan R, Santesso N, Lowe D, Hill S, Grimshaw J, Prictor M, et al. Interventions to improve safe and effective medicines use by consumers: an overview of systematic reviews. Cochrane Database Syst Rev. 2014;(4):CD007768.
21. Folkehelseinstituttet. Direkte observert behandling (DOT) [Search performed 16 Mar 2018]. https://www.fhi.no/globalassets/dokumenterfiler/rapporter/folkehelserapporten-2014-pdf.pdf (pp. 80–83).
22. Hart JE, Jeon CY, Ivers LC, Behforouz HL, Caldas A, Drobac PC, et al. Effect of directly observed therapy for highly active antiretroviral therapy on virologic, immunologic, and adherence outcomes: a meta-analysis and systematic review. J Acquir Immune Defic Syndr. 2010;54(2):167–79.
23. Persu A, Jin Y, Azizi M, Baelen M, Volz S, Elvan A, et al. Blood pressure changes after renal denervation at 10 European expert centers. J Hum Hypertens. 2014;28(3):150–6.
24. Burnier M, Wuerzner G, Struijker-Boudier H, Urquhart J. Measuring, analyzing, and managing drug adherence in resistant hypertension. Hypertension. 2013;62(2):218–25.
25. World Health Organization 2003. Adherence to long-term therapies: evidence for action [Search performed 02 May 2016]. http://www.who.int/chp/knowledge/publications/adherence_report/en/. Accessed 16 Mar 2018.
26. Waeber B, Feihl F. Assessment of drug compliance in patients with high blood pressure resistant to antihypertensive therapy. EuroIntervention. 2013;9 Suppl R:R29–34.
27. Rosa J, Widimsky P, Tousek P, Petrak O, Curila K, Waldauf P, et al. Randomized comparison of renal denervation versus intensified pharmacotherapy including spironolactone in true-resistant hypertension: six-month results from the Prague-15 study. Hypertension. 2015;65(2):407–13.
28. Azizi M, Sapoval M, Gosse P, Monge M, Bobrie G, Delsart P, et al. Optimum and stepped care standardised antihypertensive treatment with or without renal denervation for resistant hypertension (DENERHTN): a multicentre, open-label, randomised controlled trial. Lancet. 2015;385(9981):1957–65.
29. Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Bohm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. Lancet. 2010;376(9756):1903–9.
30. Bhatt DL, Kandzari DE, O'Neill WW, D'Agostino R, Flack JM, Katzen BT, et al. A controlled trial of renal denervation for resistant hypertension. N Engl J Med. 2014;370(15):1393–401.
31. Kario K, Ogawa H, Okumura K, Okura T, Saito S, Ueno T, et al. SYMPLICITY HTN-Japan—first randomized controlled trial of catheter-based renal denervation in Asian patients. Circ J. 2015;79(6):1222–9.
32. Desch S, Okon T, Heinemann D, Kulle K, Rohnert K, Sonnabend M, et al. Randomized sham-controlled trial of renal sympathetic denervation in mild resistant hypertension. Hypertension. 2015;65(6):1202–8.
33. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2009 [Search performed 25 Mar 2016]. http://prismastatement.org/. Accessed 16 Mar 2018.
34. Grant MJ, Booth A. A typology of reviews: an analysis of 14 review types and associated methodologies. Health Infor Libr J. 2009;26(2):91–108.

35. International Committee of Medical Journal Editors (ICMJE). http://www.icmje.org/recommendations/browse/publishing-andeditorial-issues/clinical-trial-registration.html. Accessed 16 Mar 2018.
36. World Health Organization. International Clinical Trials Registry Platform (ICTRP). http://www.who.int/ictrp/network/primary/en/. Accessed 16 Mar 2018.
37. US National Library of Medicine National Institutes of Health [Search performed 31 Mar 2016]. http://www.ncbi.nlm.nih.gov/pubmed. Accessed 16 Mar 2018.
38. Ovid MEDLINE [Search performed 31 Mar 2016]. http://ovidsp.ovid.com/. Accessed 16 Mar 2018.
39. The Cochrane Library [Search performed 31 Mar 2016]. http://www.cochranelibrary.com/. Accessed 16 Mar 2018.
40. EMBASE [Search performed 31 Mar 2016]. https://www.elsevier.com/solutions/embase-biomedical-research. Accessed 16 Mar 2018.
41. Clinical Trials Gov. [Search performed 4 Jan 2016]. https://clinicaltrials.gov/ct2/results?cond=%22Hypertension%22. Accessed 16 Mar 2018.
42. International Standard Randomized Clinical Trial Number [Search performed 23 Mar 2016]. http://www.isrctn.com/search?q=. Accessed 16 Mar 2018.
43. EU Clinical Trials Register [Search performed 31 Mar 2016]. https://www.clinicaltrialsregister.eu/ctr-search/search. Accessed 16 Mar 2018.
44. German Clinical Trials Register [Search performed 23 Mar 2016]. https://www.drks.de/drks_web/setLocale_EN.do. Accessed 16 Mar 2018.
45. Netherlands Trial Register [Search performed 23 Mar 2016]. http://www.trialregister.nl/trialreg/index.asp. Accessed 16 Mar 2018.
46. Australian New Zealand Clinical Trials Regestry [Search performed 23 Mar 2016]. http://www.anzctr.org.au/TrialSearch.aspx. Accessed 16 Mar 2018.
47. Brazilian Registry of Clinical Trials [Search performed 23 Mar 2016]. http://www.ensaiosclinicos.gov.br/. Accessed 16 Mar 2018.
48. Chinese Clinical Trial Register (ChiCTR) [Search performed 23 Mar 2016]. http://www.chictr.org.cn/abouten.aspx. Accessed 16 Mar 2018.
49. Clinical Research Information Service (CRIS)—Korea 2016 [Search performed 23 Mar 2016]. http://www.who.int/ictrp/network/cris2/en/index1.html. Accessed 16 Mar 2018.
50. Clinical Trials Registry India (CTRI) [Search performed 23 Mar 2016]. http://ctri.nic.in/Clinicaltrials/login.php. Accessed 16 Mar 2018.
51. The Pan African Clinical Trials Registry (PACTR) [Search performed 23 Mar 2016]. http://www.pactr.org/. Accessed 16 Mar 2018.
52. Cuban Registry of Clinical Trials (RPCEC) [Search performed 23 Mar 2016]. http://registroclinico.sld.cu/en/home. Accessed 16 Mar 2018.
53. Iranian Registry of Clinical Trials (IRCT) [Search performed 23 Mar 2016]. http://irct.ir/. Accessed 16 Mar 2018.
54. Miroslawska A, Solbu M, Skjolsvik E, Toft I, Steigen TK. Renal sympathetic denervation: effect on ambulatory blood pressure and blood pressure variability in patients with treatment-resistant hypertension. The ReShape CV-risk study. J Hum Hypertens. 2016;30(3):153–7.
55. EU Clinical Trials Register EudraCT2005-001004-39 [Search performed 23 Mar 2016]. https://www.clinicaltrialsregister.eu/ctrsearch/trial/2005-001004-39/GB#A. Accessed 16 Mar 2018.
56. EU Clinical Trials Register EudraCT2013-001227-40 [Search performed 23 Mar 2016]. https://www.clinicaltrialsregister.eu/ctrsearch/trial/2013-001227-40/NO#A. Accessed 16 Mar 2018.
57. ISRCTN57475376 Diagnosing and treating severe hypertension [Search performed 23 Mar 2016]. http://www.isrctn.com/search?q=directly+observed+therapy&filters=condition%3Acir-culatory+system&searchType=advanced-search. Accessed 16 Mar 2018.
58. ClinicalTrialGov NCT02362893 Treatment of hypertension: an interventional approach to improve blood pressure control (DRIVE) [Searched performed 23 Mar 2016]. https://clinicaltrials.gov/ct2/show/NCT02362893?term=nct02362893&rank=1. Accessed 16 Mar 2018.

59. ClinicalTrialGov NCT02513524 Prevalence of resistant hypertension with DOT (DOT) [Search performed 23 Mar 2016]. https://clinicaltrials.gov/ct2/show/NCT02513524. Accessed 16 Mar 2018.
60. Ruzicka M, Hiremath S. Can drugs work in patients who do not take them? The problem of non-adherence in resistant hypertension. Curr Hypertens Rep. 2015;17(9):579.
61. Eskas PA, Heimark S, Eek Mariampillai J, Larstorp AC, Fadl Elmula FE, Hoieggen A. Adherence to medication and drug monitoring in apparent treatment-resistant hypertension. Blood Press. 2016;25(4):199–205.
62. Ruzicka M, McCormick B, Leenen FH, Froeschl M, Hiremath S. Adherence to blood pressure-lowering drugs and resistant hypertension: should trial of direct observation therapy be part of preassessment for renal denervation? Can J Cardiol. 2013;29(12):1741.e1–3.
63. Brown MJ. Resistant hypertension: resistance to treatment or resistance to taking treatment? Heart. 2014;100(11):821–2.
64. McCormack GR, Virk JS. Driving towards obesity: a systematized literature review on the association between motor vehicle travel time and distance and weight status in adults. Prev Med. 2014;66:49–55.
65. The Cochrane Collaboration [Search performed 10 May 2016]. http://www.cochrane.org/. Accessed 16 Mar 2018.
66. The Campbell Collaboration [Search performed 10 May 2016]. http://www.campbellcollaboration.org/. Accessed 16 Mar 2018.
67. Godlee F. The Cochrane Collaboration. BMJ. 1994;309(6960):969–70.
68. Griffin BR, Schinstock CA. Thinking beyond new clinical guidelines: update in hypertension. Mayo Clin Proc. 2015;90(2):273–9.
69. Altman DG. Practical statistics for medical research. London: Chapman and Hall; 1991. XII, 611 s. : ill. p.
70. Ghofrani H, Weaver FA, Nadim MK. Resistant hypertension: medical management and alternative therapies. Cardiol Clin. 2015;33(1):75–87.
71. Lemstra M, Alsabbagh MW. Proportion and risk indicators of nonadherence to antihypertensive therapy: a meta-analysis. Patient Prefer Adherence. 2014;8:211–8.
72. Matthes J, Albus C. Improving adherence with medication: a selective literature review based on the example of hypertension treatment. Deutsch Arztebl Int. 2014;111(4):41–7.
73. Marshall IJ, Wolfe CDA, McKevitt C. Lay perspectives on hypertension and drug adherence: systematic review of qualitative research. BMJ. 2012;345:e3953.
74. Chen SL, Lee WL, Liang T, Liao IC. Factors associated with gender differences in medication adherence: a longitudinal study. J Adv Nurs. 2014;70(9):2031–40.
75. Gwadry-Sridhar FH, Manias E, Lal L, Salas M, Hughes DA, Ratzki-Leewing A, et al. Impact of interventions on medication adherence and blood pressure control in patients with essential hypertension: a systematic review by the ISPOR medication adherence and persistence special interest group. Value Health. 2013;16(5):863–71.
76. Rosenbaum L. Beyond belief—how people feel about taking medications for heart disease. N Engl J Med. 2015;372(2):183–7.
77. Zheng S, Nath V, Coyne DW. ACE inhibitor-based, directly observed therapy for hypertension in hemodialysis patients. Am J Nephrol. 2007;27(5):522–9.
78. Kalra S, Gupta Y. DOT (directly observed therapy) in diabetes: current thought, future reality. Aust J Rural Health. 2014;22(4):206.
79. Cioe PA, Stein MD, Promrat K, Friedmann PD. A comparison of modified directly observed therapy to standard care for chronic hepatitis C. J Community Health. 2013;38(4):679–84.
80. Deen R. Use of direct observed therapy to confirm compliance in a warfarin clinic. J Patient Saf. 2011;7(4):232–3.
81. Zimmerman N. Telemonitoring of medication adherence in patients with major mental illness: watching the patient as well as the pills. Stud Health Technol Inform. 2012;182:189–96.
82. Heimark S, Eskas PA, Mariampillai JE, Larstorp AC, Hoieggen A, Fadl Elmula FE. Tertiary work-up of apparent treatment-resistant hypertension. Blood Press. 2016;25(5):312–8.

83. Persu A, Jin Y, Baelen M, Vink E, Verloop WL, Schmidt B, et al. Eligibility for renal denervation: experience at 11 European expert centers. Hypertension. 2014;63(6):1319–25.
84. Mariampillai JE, Eskås PA, Heimark S, Larstorp ACK, Fadl Elmula FEM, Høieggen A, Nortvedt P. Apparent treatment-resistant hypertension—patient.physician relationship and ethical issues. Blood Press. 2017;26:133–8.
85. McCambridge J, Witton J, Elbourne DR. Systematic review of the Hawthorne effect: new concepts are needed to study research participation effects. J Clin Epidemiol. 2014;67(3):267–77.
86. Kvale S, Brinkmann S, Anderssen TM, Jf R. Det kvalitative forskningsintervju. Oslo: Gyldendal akademisk; 2009. 344 s.: ill. p.

Digital Medicines to Measure Drug Ingestion Adherence

7

Naunihal S. Virdi

7.1 Introduction

Usual methods for measuring medication adherence use indirect methods such as refill data, pill counts, smart pill caps, surveys, and use of serum or urine drug levels [1]. These methods make inferences about regular medication-taking and can be inaccurate. Additionally, they do not allow providers to make timely interventions, and patients are unable to receive regular, prompt feedback on their medication-taking behaviors.

Direct methods for measuring adherence can resolve problems that exist with indirect measures. Until recently, directly observing ingestion was the only validated method to be certain a medication was taken. However, this method is impractical except in certain clinical situations such as hospitalization, nursing home residency, imprisonment, and the expensive measures employed in treating tuberculosis.

Recent evidence has demonstrated the lack of effectiveness in using passive means for measuring adherence such as smart caps on pill bottles [2, 3]. In his book, "Thinking Fast and Slow," Kahneman reports that people are poor intuitive statisticians [4]. Put in a healthcare context, individuals underestimate their own risk for a particular outcome, such as myocardial infarction or stroke. Additionally, the benefit of antihypertensive and other cardiovascular medications is often preventing future complications, rather than direct relief of symptoms. This may lead patients to believe that these medications have less of an immediate, tangible value.

Patients with greater levels of engagement in their care utilize fewer healthcare resources [5, 6]. Reaching a mutual agreement on an identifiable treatment goal and providing a feedback loop for patients and providers can reinforce the importance

N. S. Virdi, M.D., F.A.C.P.
Proteus Digital Health, Redwood City, CA, USA
e-mail: nvirdi@proteus.com

M. Burnier (ed.), *Drug Adherence in Hypertension and Cardiovascular Protection*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-76593-8_7

of adherence, and engage patients in their own healthcare plan. Providers can also focus their attention on making specific and timely medical decisions, such as medication changes or titration, lifestyle modifications, and adherence counseling.

7.2 Digital Medicines

Proteus Discover™ (Proteus Digital Health®, Redwood City, CA) was designed specifically to provide feedback on medication adherence, as well as other health-related metrics to both patients and providers. Discover™ is FDA cleared and consists of tiny ($1.0 \times 1.0 \times 0.3$ mm) ingestible sensors to allow for the direct measurement of medication ingestion adherence when taken with medication, a wearable sensor patch, and software on a mobile device [7, 8]. The ingestible sensor is composed of common dietary minerals (silicon, copper, and magnesium) and can be combined with a patient's medication to create digital medicines utilizing one of the two methods: (1) the ingestible sensor is incorporated into a placebo pill and swallowed at the same time as the medication (e.g., through co-encapsulation with the medication by a pharmacist acting on a physician's order) or (2) integrated within the medication during the medication's manufacturing process [1]. Data generated by Proteus Discover can be accessed by patients, caregivers, and providers via a mobile app and web portal.

Once the sensor is ingested, the magnesium and copper layers become wet, triggering an electrochemical reaction that powers the circuit inside the sensor (the same principle governing operation of a "potato battery"). Once activated, the sensor sends a unique message coded for the medication name and dose to a wearable sensor patch worn on the patient's torso, and records the date and time of the sensor ingestion. The electrical signal continues until the electrochemically active material is exhausted (in a few minutes). The ingestible sensor ultimately passes through the digestive system and is eliminated as waste [7].

The disposable wearable sensor patch may be worn for up to 7 days, and in addition to ingestible sensor data also collects information on body position (e.g., sitting, standing, lying), step count, rest duration, and heart rate. The information collected by the patch is encrypted and wirelessly transmitted via Bluetooth to a designated mobile device, which forwards it to a secure data server/cloud [7, 8]. A mobile device app summarizes the information collected by the patch. Healthcare providers, family members, caregivers, or others authorized by the patient can access the Proteus data and analytics through a secure online portal or via secure notifications. Figure 7.1 illustrates the data flow through Proteus Discover.

The mobile device software application also has features to engage patients in their self-management. Patients can set up their medication schedule, including reminders and text messages, for themselves, their family or friends. The text messages can remind patients to take their medications, change the patch, or to ensure they are close to the mobile device so that data can continue to flow. Another feature prompts patients who miss medication doses with a survey to assess reasons for missing the dose (e.g., forgot to take the medication dose, concern about side effects, or lack of supply).

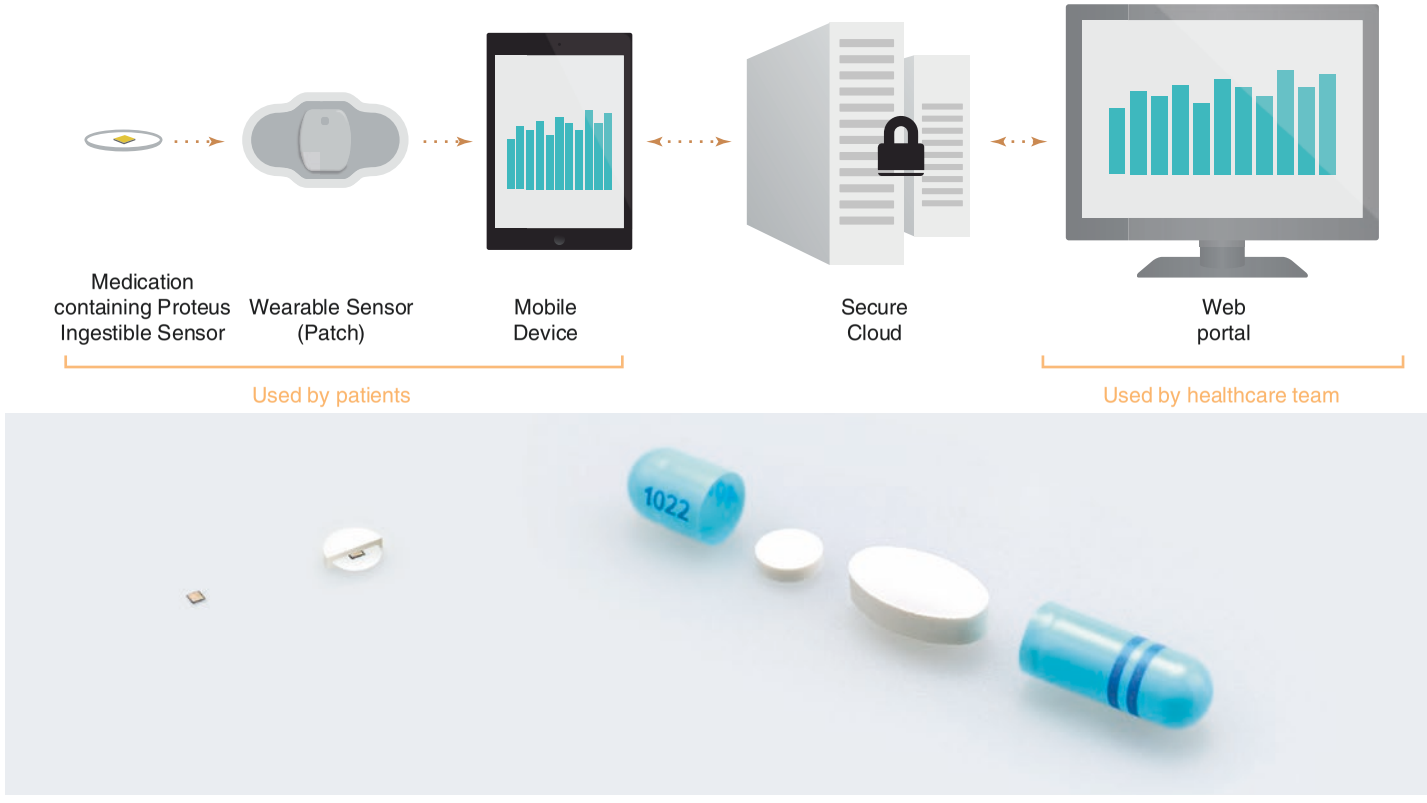


Fig. 7.1 Top: illustration of the components of Proteus Discover. Bottom: the Proteus ingestible sensor pill and a digitized medication

7.3 Pre-approval Studies

De novo 510K clearance in the US and CE mark in the EU occurred after many preclinical and clinical studies that were conducted to ensure safety and effectiveness.

Benchtop and animal studies confirmed the ingestible sensor was safe with regard to toxicology, mechanical, and electrical safety. These studies also confirmed that all ingestible sensors were eliminated as solid waste within 72 h. Additionally, one study confirmed that the electrical signal from the ingestible sensor was not significantly affected by changes in local pH (from 1.6 to 7), or varying the concentration of potassium, chloride, or pepsin [8].

Early clinical studies with the ingestible sensor were performed in 412 volunteers from various populations (healthy subjects, and in subjects with hypertension, heart failure, tuberculosis, bipolar affective disorder, or schizophrenia) and 20,933 ingestions. These studies reconfirmed the safety profile. Of 324 directly observed ingestions, the average positive detection accuracy was 99.1% (95% confidence interval of 97.3–99.7%); there were no false positive detections. Studies also confirmed the ability of the device to detect multiple ingestible sensors taken at the same time. The most common side effects from the ingestible sensor were nausea/vomiting (1%) and constipation (0.5%) [8].

The safety of the wearable sensor was also tested in the same populations above and in additional populations (e.g., the elderly). Overall, 492 subjects (age range 21–85 years old, mean: 44.6 years old), who wore the patch for a total of 6407 patch-use days. The most common issues reported were cutaneous adverse events. Sixty-one (12.4% of the 492 subjects) experienced self-limited rashes localized at the site of patch placement [9].

7.4 Early Clinical Experience

An early commercial experiment included patients with hypertension in the outpatient setting in the United Kingdom. Healthcare providers prescribed a 2-week use of the Proteus patch with the Proteus pill that was co-ingested with their usual antihypertensive medications. This allowed the patients and providers to understand the root cause for uncontrolled hypertension. During this time, patients did not receive feedback on their ingestions; however, after the patches were downloaded, both the patient and provider could review the data together.

Drs. Godbehere and Wareing described use in eight patients; all saw decreases in blood pressure. Additionally, the Proteus data improved medical decision-making, with four patients receiving dose titrations and three patients given specific adherence counseling [10].

A commercial pilot was also conducted with pharmacists at 15 sites across the Isle of Wight in the United Kingdom. Patients with uncontrolled blood pressure were prescribed the Digital Health Feedback Device for 2 weeks. A root cause of elevated blood pressure was determined in all 39 patients: 68% required medication titration (higher doses or additional medication) and 32% were found to just need adherence counseling. The Proteus data also helped to guide physical activity recommendations [11].

Patients in the Isle of Wight pilot reported having a positive experience overall. Most patients rated the Proteus device highly in terms of ease of patch attachment, use of the patch, app usability and usefulness. Additionally, 87% felt more involved in their own care, and 87% also found the information helped to improve their treatment adherence. Pharmacists also had positive feedback, with 91% stating that Proteus helped guide clinical decision-making [11].

7.5 Clinical Studies in Hypertension

7.5.1 UK Hypertension Registry Study [12]

This study largely followed the initial UK clinical experience. Subjects with uncontrolled hypertension were enrolled across six primary care clinics in the Midlands of England. All subjects had failed at least two antihypertensives. Subjects used the Proteus patch and co-ingested the Proteus pill along with their antihypertensive medications.

Of the 151 subjects enrolled, 144 completed the study and were included in the efficacy analysis. More than half of enrolled subjects were male (58%) and the mean age was 68 (SD 9, range 31–90 years old). More than half (62%) of subjects used two antihypertensives, with the remaining subjects using more than two agents.

A root cause for uncontrolled hypertension was determined in all 144 subjects who completed the study. Of the 144 subjects, 46 (32%) achieved blood pressure control (<140/90 mmHg). On average, the systolic and diastolic blood pressure values changed by −9.7 (95% CI −12.5, −7.0, baseline 154 ± 13) mmHg and −5.0 (95% CI −6.5, −3.5, baseline 85 ± 11) mmHg.

The subjects rated their experience highly. Most (92%) did not mind wearing the patch and expressed willingness to wear it repeatedly and for longer periods. A similar proportion reported the Proteus concept was easy to understand and using Proteus was convenient. Overall, 87% of subjects reported they had a good experience using the Proteus device.

Providers were similarly satisfied. Most practices (75%) found that the use of the ingestible sensor added value to their practice, improved the conversations about hypertension treatment with their patients, and helped them stay connected with their patients.

7.5.2 US Pilot Study in Hypertension and Diabetes

US Cluster-Randomized Pilot-Study in Patients with Uncontrolled Hypertension and Type 2 Diabetes [13].

As a follow-on to the UK Hypertension Registry Study, Proteus conducted a study in patients to assess patients' response to medical interventions made by providers after review of their clinical and adherence data. Participants were selected after having an elevated systolic blood pressure (≥140 mmHg) and glycated

Table 7.1 Digital medication panel for hypertension and Type 2 diabetes study

Medication	Doses available (mg)
Antihypertensive	
Lisinopril	10, 20, 40
Losartan	100
Hydrochlorothiazide	12.5, 25
Amlodipine	5
Antidiabetic	
Metformin	500
Glipizide	5
Statin	
Atorvastatin	20

hemoglobin (A1C $\geq$ 7%), after failing at least two antihypertensives from the medication panel (medications from the same drug classes at similar doses was also acceptable) and metformin and/or glipizide. Subjects used the Proteus Discover offering with digital antihypertensive, antidiabetic, and statin medicines. Table 7.1 lists the medications and doses available during the study. If necessary, the subject could take more than one capsule of each medication during a dosing session (e.g., the subject could take two metformin 500 mg capsules).

There were 13 sites that were randomized to one of the three treatment arms: Proteus Discover with Digital Medicines use for 4 weeks (DM4), Proteus Discover with Digital Medicines use for 12 weeks (DM12), and usual care. All subjects were followed for 12 weeks. Clinical outcomes of interest were change in blood pressure at Weeks 4 and 12 (change in systolic blood pressure at Week 4 was the primary outcome), change in A1C at Week 12, and change in low density lipoprotein cholesterol (LDL-C) at Weeks 4 and 12 in those who were using statin therapy. Since both DM arms received the same intervention during the first 4 weeks, they were combined for analyses performed at Week 4.

The analyzed population included 109 subjects (40 in each of the DM arms and 29 in the usual care arm). Table 7.2 summarizes the demographics and baseline characteristics for the study population.

After 4 weeks, there was a significantly greater reduction in systolic blood pressure in the DM arm (−21.8 ± 1.5 mmHg) compared with the usual care arm (−12.7 ± 2.8 mmHg). DM12 subjects continued to have a further decrease in their systolic blood pressure (−24.6 ± 1.7 mmHg), which remained statistically greater than the reduction in systolic blood pressure for the usual care arm (−15.2 ± 2.0 mmHg). The DM arms had nonsignificant differences in change in A1C compared with usual care (−0.32 ± 0.22% for DM4, −0.08 ± 0.22% for DM12, 0.28 ± 0.35%for usual care). For subjects with a baseline A1C ≥8%, both DM arms had larger A1C decreases (−0.72 ± 0.23% for DM4 and −0.31 ± 0.31% for DM12); whereas, the usual care arm had an increase in A1C (0.26 ± 0.34%). A summary of the main clinical results is found in Fig. 7.2.

During the study, subjects in the DM arms had a high adherence rate of 84% for the 12 weeks (data available for the DM12 arm only) and 86% during the first 4 weeks. This level of adherence is higher than the average level of adherence to chronic medications of <50% for patients in general.

Table 7.2 Demographics and baseline characteristics of the study population

	DM4 ($n = 40$)	DM12 ($n = 40$)	DM (Both arms) ($n = 80$)	Usual care ($n = 29$)
N	40	40	80	29
Age (years, mean ± SE)	58.8 ± 1.38	56.7 ± 1.80	57.8 ± 1.13	61.6 ± 1.70
Female (%)	52.5%	60.0%	56.3%	34.5%
African American (%)	27.5%	7.5%	17.5%	10.3%
Caucasian (%)	72.5%	60.0%	66.3%	65.5%
Asian (%)	0.0%	32.5%	16.3%	6.9%
Hispanic ethnicity (%, includes all races)	55.0%	37.5%	46.3%	44.8%
Income ≤$20,000 (%)	57.5%	52.5%	55.0%	62.1%
Education < high school (%)	45.0%	15.0%	30.0%	34.5%
Employed (%)	45.0%	60.0%	52.5%	31.0%
Weight (kg, mean ± SE)	91.5 ± 5.91	85.7 ± 3.41	88.6 ± 3.34	89.7 ± 4.67
BMI (kg/m^2, mean ± SE)	32.8 ± 1.37	30.7 ± 0.91	31.8 ± 0.89	31.3 ± 0.97
Systolic BP (mmHg, mean ± SE)	152.2 ± 1.57	146.5 ± 0.80[a]	149.3 ± 1.46[a]	155.4 ± 2.97
Diastolic BP (mmHg, mean ± SE)	90.5 ± 2.79	82.0 ± 5.14	86.2 ± 3.20	83.9 ± 2.94
A1C (%, mean ± SE)	8.8 ± 0.29	8.5 ± 0.20	8.7 ± 0.18	8.3 ± 0.38
LDL-C (mg/dL, mean ± SE)	110.7 ± 5.29	107.1 ± 6.61	108.9 ± 3.91	99.1 ± 6.16
HDL-C (mg/dL, mean ± SE)	47.8 ± 2.55	45.2 ± 1.47	46.5 ± 1.44	40.6 ± 2.51
Triglycerides (mg/dL, mean ± SE)	211.2 ± 28.09	195.7 ± 17.30	203.4 ± 16.22	226.1 ± 36.19
Total cholesterol (mg/dL, mean ± SE)	190.2 ± 6.50	175.3 ± 6.03	182.8 ± 4.46	174.4 ± 13.17

[a]Difference compared to Usual Care is statistically significant (p value <0.05). Note differences in demographics did not alter outcomes

As seen in the previous studies, subject satisfaction with Proteus Discover was rated highly. Subjects agreed that Proteus Discover was easy to use and learn. They also felt that being able to see the data motivated them to improve their health and have more helpful conversations with their healthcare providers.

7.6 Real-World Evidence

Proteus Discover was introduced into customer settings as an aid to improve control of diabetes, hypertension, and hypercholesterolemia. A retrospective analysis on patients with uncontrolled hypertension was performed in a community setting at a health system in California. Data was available on 53 patients who were prescribed Proteus Discover (mean age of 62 years, 52% male, 79% white). Patients used Proteus Discover for an average of 34 days with a mean medication ingestion adherence of 87% and high patch use of 94% during the 34 days. Patients realized sustained reductions in both systolic (9.4 mmHg, $P < 0.001$) and diastolic (5.7 mmHg, $P < 0.001$) blood pressure during the entire follow-up period (mean of 165 days after stopping use of Proteus Discover).

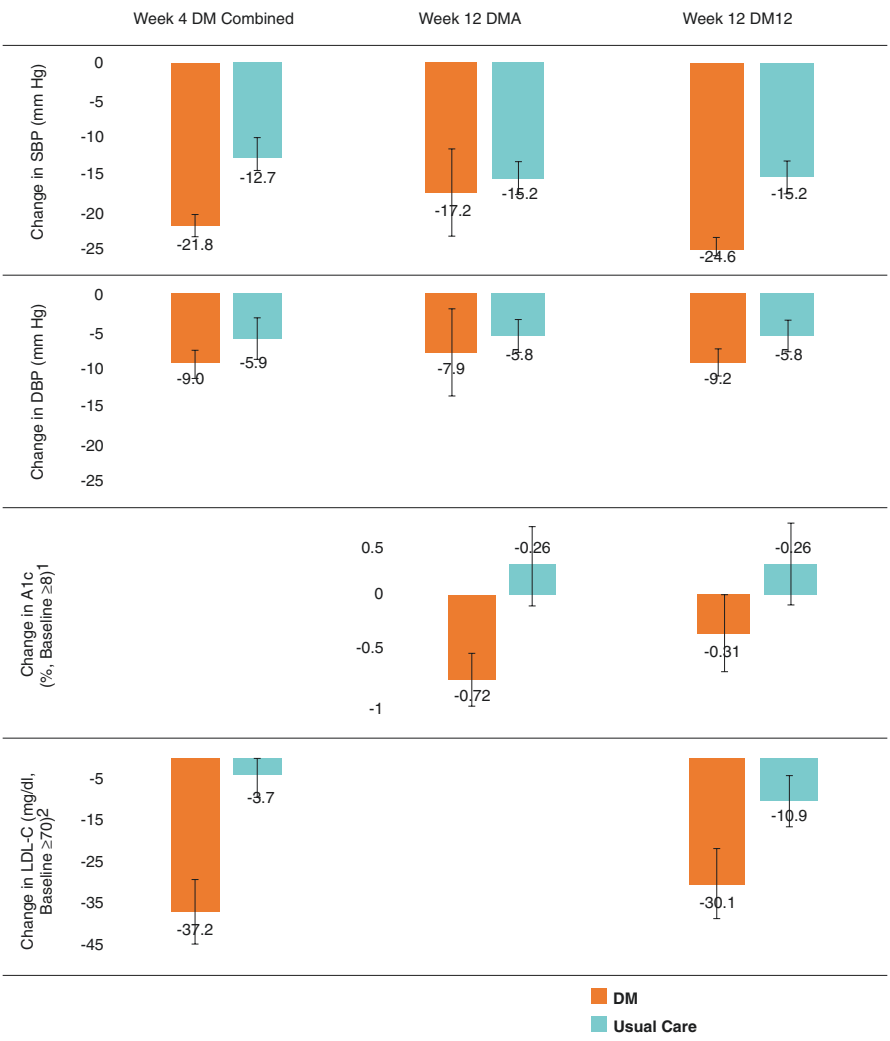


Fig. 7.2 Summary of clinical results [Note this figure was published and can be reproduced under the terms of Creative Commons Attribution 4.0 license for the article referenced for this study]. [1]*N* = 65 (DMO-4: 26, DMO-12: 24, and UC: 15). (a) DMO-4 – UC: −0.98 (−1.72, −0.24). (b) DMO-12 –UC: −0.57 (−1.53, 0.39). [2]*N* = 54 (DMO-4: 6, DMO-12: 28, UC: 20). (a) Week 4: DMO – UC: −33.2 (−50.6, −15.8). (b) −19.2 (−36.4, −2.0) at Week 12. Due to small sample size, both DMO groups were combined at Week 12

Additional analyses showed a reduction in A1C (1.06%, n = 13, P = 0.02) and LDL (48.9 mg/dL, n = 7, P = 0.05). There was an early downward (~37% reduction) in ER visits (n = 53, P = 0.280). Most patients agreed that Proteus Discover was easy to use (86%) and helped them improve their health (89%) [14].

7.7 Experience in Other Therapeutic Areas

Medication adherence is also critical to clinical management of conditions other than hypertension and diabetes mellitus [15–21]. The Proteus technology has been used successfully in other therapeutic areas including mental health, infectious diseases, and pulmonary arterial hypertension. In these studies, patients responded positively to the Proteus technology.

First, in mental health, a 4-week, observational study was run in subjects with bipolar disorder [12] or schizophrenia [18], who used an older version of the Proteus technology. Subjects achieved an average medication ingestion adherence of 74%. Most (89%) found the system useful to them, with 78% stating they liked to receive reminders if they forgot to take their medicine [22].

Among infectious diseases, Proteus has been involved in three studies. The first was a study in tuberculosis that was completed prior to FDA approval of the Proteus device and helped to confirm the system's accuracy and safety profile [23]. A larger tuberculosis study was conducted at a major academic medical center as well as a smaller pilot study done in hepatitis C [24, 25]. The final results are still pending for both studies. Interim results indicate that the system was useful in promoting ingestion adherence in this diverse and challenging population.

For the hepatitis C study in particular, 28 subjects were enrolled and many had risk factors for nonadherence (11 history of drug abuse and 13 had psychiatric comorbidities). The average ingestion adherence was 94% and the data facilitated targeted and timely interventions in 11 patients [25].

Finally, Proteus Discover was used in patients with pulmonary arterial hypertension in a 12-week, 21-subject, prospective study. In addition to promoting a high level of ingestion adherence (mean adherence 94%), the study also found a correlation between step count and adherence. The ingestion adherence data was also used to guide therapeutic decision-making [26].

7.8 Future Directions

Because nonadherence is a pervasive issue throughout chronic disease management, Proteus Discover is being introduced in other therapeutic areas. In late 2015 and early 2016, the company began working with three leading institutions on multi-year NIH-funded studies to measure adherence in HIV patients and patients initiating HIV pre-exposure prophylaxis [27–29].

Conclusion

Evidence has shown that simple reminders and retrospective measurements of adherence are not enough to promote changes in adherence behavior. Timely and accurate feedback to patients promotes healthy behaviors and medication adherence and offers reliable data to providers for making more informed decisions. By delivering a direct measurement of medication adherence and timely

feedback to patients and providers, Proteus Discover better supports provider decision-making and patient engagement in their self-care, thereby improving treatment outcomes.

Acknowledgements The author would like to acknowledge the following persons for their editorial support: Scooter Plowman, Betsy Klein, Praveen Raja, Melody Tran, George Savage, Lorenzo DiCarlo, Andrew Thompson, Maneesh Gupta, David O'Reilly, Manny Severino, and Lacey Kim.

References

1. Rohatagi S, Profit D, Hatch A, Zhao C, Docherty JP, Peters-Strickland TS. Optimization of a digital medicine system in psychiatry. J Clin Psychiatry. 2016;77(9):e1101–7. https://doi.org/10.4088/JCP.16m10693.
2. Choudhry NK, Krumme AA, Ercole PM, Girdish C, Tong AY, Khan NF, Brennan TA, Matlin OS, Shrank WH, Franklin JM. Effect of reminder devices on medication adherence: the REMIND randomized clinical trial. JAMA Intern Med. 2017;177(5):624. https://doi.org/10.1001/jamainternmed.2016.9627.
3. Choudhry NK, Krumme AA, Ercole PM, Girdish C, Isaman DL, Matlin OS, Brennan TA, Shrank WH, Franklin JM. Rationale and design of the randomized evaluation to measure improvements in non-adherence from low-cost devices (REMIND) trial. Contemp Clin Trials. 2015;43:53–9. https://doi.org/10.1016/j.cct.2015.05.006.
4. Kahneman D. Thinking, fast and slow. 1st ed. New York: Farrar, Straus and Giroux; 2011.
5. Hibbard JH, Greene J, Overton V. Patients with lower activation associated with higher costs; delivery systems should know their patients' "scores". Health Aff Proj Hope. 2013;32(2):216–22. https://doi.org/10.1377/hlthaff.2012.1064.
6. Remmers C, Hibbard J, Mosen DM, Wagenfield M, Hoye RE, Jones C. Is patient activation associated with future health outcomes and healthcare utilization among patients with diabetes? J Ambulatory Care Manage. 2009;32(4):320–7. https://doi.org/10.1097/JAC.0b013e3181ba6e77.
7. DiCarlo L, Moon G, Intondi A, Duck R, Frank J, Hafazi H, Behzadi Y, Robertson T, Costello B, Savage G, Zdeblick M. A digital health solution for using and managing medications: wirelessly observed therapy. IEEE Pulse. 2012;3(5):23–6. https://doi.org/10.1109/MPUL.2012.2205777.
8. Hafezi H, Robertson TL, Moon GD, Au-Yeung K-Y, Zdeblick MJ, Savage GM. An ingestible sensor for measuring medication adherence. IEEE Trans Biomed Eng. 2015;62(1):99–109. https://doi.org/10.1109/TBME.2014.2341272.
9. Proteus digital health feedback device, instructions for use. Redwood City, CA: Proteus(r) Digital Health, Inc.; 2016.
10. Godbehere P, Wareing P. Hypertension assessment and management: role for digital medicine. J Clin Hypertens (Greenwich). 2014;16(3):235. https://doi.org/10.1111/jch.12246.
11. Noble K, Brown K, Medina M, Alvarez F, Young J, Leadley S, Kim Y, DiCarlo L. Medication adherence and activity patterns underlying uncontrolled hypertension: assessment and recommendations by practicing pharmacists using digital health care. J Am Pharm Assoc. 2016;56(3):310–5. https://doi.org/10.1016/j.japh.2016.01.005.
12. Naik R, Macey N, West RJ, Godbehere P, Thurston S, Fox R, Xiang W, Kim YA, Singh I, Leadley S, DiCarlo LA. First use of an ingestible sensor to manage uncontrolled blood pressure in primary practice: the UK hypertension registry. J Community Med Health Educ. 2017;7(1). https://doi.org/10.4172/2161-0711.1000506.
13. Frias J, Virdi N, Raja P, Kim Y, Savage G, Osterberg L. Effectiveness of digital medicines to improve clinical outcomes in patients with uncontrolled hypertension and type 2

diabetes: Prospective, Open-Label, Cluster-Randomized Pilot Clinical Trial. J Med Internet Res 2017;19(7):e246. DOI:10.2196/jmir.7833.
14. Pidermann B, Park H, Bijlani A, Truscott A, Travis E, Purvance C. The first real-world clinical and health economic outcomes of a digital health offering in a patient population with cardiovascular and metabolic chronic diseases. J Manag Care Spec Pharm 2017;23(3-a):S68.
15. Pinsky BW, Takemoto SK, Lentine KL, Burroughs TE, Schnitzler MA, Salvalaggio PR. Transplant outcomes and economic costs associated with patient noncompliance to immunosuppression. Am J Transplant. 2009;9(11):2597–606. https://doi.org/10.1111/j.1600-6143.2009.02798.x.
16. Zullig LL, Peterson ED, Bosworth HB. Ingredients of successful interventions to improve medication adherence. JAMA. 2013;310(24):2611–2. https://doi.org/10.1001/jama.2013.282818.
17. Lin S, Melendez-Torres GJ. Systematic review of risk factors for nonadherence to TB treatment in immigrant populations. Trans R Soc Trop Med Hyg. 2016;110(5):268–80. https://doi.org/10.1093/trstmh/trw025.
18. Lee WC, Balu S, Cobden D, Joshi AV, Pashos CL. Prevalence and economic consequences of medication adherence in diabetes: a systematic literature review. Manag Care Interface. 2006;19(7):31–41.
19. Claborn KR, Meier E, Miller MB, Leffingwell TR. A systematic review of treatment fatigue among HIV-infected patients prescribed antiretroviral therapy. Psychol Health Med. 2015;20(3):255–65. https://doi.org/10.1080/13548506.2014.945601.
20. Ascher-Svanum H, Faries DE, Zhu B, Ernst FR, Swartz MS, Swanson JW. Medication adherence and long-term functional outcomes in the treatment of schizophrenia in usual care. J Clin Psychiatry. 2006;67(3):453–60.
21. Blaschke TF, Osterberg L, Vrijens B, Urquhart J. Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories. Annu Rev Pharmacol Toxicol. 2012;52:275–301. https://doi.org/10.1146/annurev-pharmtox-011711-113247.
22. Kane JM, Perlis RH, DiCarlo LA, Au-Yeung K, Duong J, Petrides G. First experience with a wireless system incorporating physiologic assessments and direct confirmation of digital tablet ingestions in ambulatory patients with schizophrenia or bipolar disorder. J Clin Psychiatry. 2013;74(6):e533–40. https://doi.org/10.4088/JCP.12m08222.
23. Belknap R, Weis S, Brookens A, Au-Yeung KY, Moon G, DiCarlo L, Reves R. Feasibility of an ingestible sensor-based system for monitoring adherence to tuberculosis therapy. PLoS One. 2013;8(1):e53373. https://doi.org/10.1371/journal.pone.0053373.
24. Wirelessly Observed Therapy (WOT): a new paradigm in TB therapy monitoring | CROI conference. http://www.croiconference.org/sessions/wirelessly-observed-therapy-wot-new-paradigm-tb-therapy-monitoring. Accessed 25 Apr 2017.
25. Bonacini M, Kim YA, Reichert M, Travis E, Virdi N, Raja P, Savage G. Tu1659 a new digital health feedback offering to keep patients adherent to oral hepatitis C therapy. Gastroenterology. 2016;150(4):S1159. https://doi.org/10.1016/S0016-5085(16)33916-6.
26. Corris PA, Day M, Gibiansky M, Kim YA, DiCarlo L. A pilot study of digital feedback to guide therapeutic decisions in pulmonary hypertension. Eur Respir J. 2016;48(Suppl 60):PA2407.
27. Measuring and monitoring adherence to ART with pill ingestible sensor system—full text view. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02797262. Accessed 9 May 2017.
28. Digital health feedback system for longitudinal measurement of medication adherence during initial ARV therapy—full text view. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02800655. Accessed 9 May 2017.
29. Feasibility of an ingestible sensor system to measure PrEP adherence in YMSM—full text view. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02891720. Accessed 9 May 2017.

Ethical Aspects of Measuring Adherence to Antihypertensive Treatment

8

Paul Hjemdahl

Poor adherence to prescribed drug therapy is a common and potentially modifiable reason for inadequate treatment effects, not least in chronic and (usually) asymptomatic conditions like hypertension [1–3]. Poor adherence is associated with worsened outcomes and it is an important task for the medical team taking care of the patient to identify and manage the problem [2]. However, assessing and improving adherence are difficult tasks and the literature on adherence in hypertension is quite diverse with estimates of non-adherence from <10% to >50% depending on methods used and populations and clinical settings studied.

Reasons for not taking medicines as prescribed are many, ranging from forgetfulness to fear of adverse effects and lack of motivation to take preventive therapy. Adverse effects are not a big problem with antihypertensive medications but when they appear—as true side effects or due to the nocebo effect—many patients will quit taking the drug(s) without consulting their physicians. Thus, it is most important to convince the patient that it is in his/her best interest to take the drug(s) prescribed upon initiation of treatment and the motivation of the patient must be maintained during long-term treatment. In studies of willingness to take cardiovascular preventive medication surprisingly many patients require large and preferably quick and certain benefits (prolongation of life or reduced risk of suffering complications) to consider starting treatment [4]. Thus, the odds are often against preventive medication. Even if we are convinced that it is in the best interest of the patient to take the treatment this is ultimately the patients' decision and doctors must respect the autonomy and integrity of the patient.

P. Hjemdahl, M.D., Ph.D., F.E.S.C., F.A.H.A.
Department of Medicine Solna, Clinical Epidemiology Unit/Clinical Pharmacology, Karolinska Institutet, Karolinska University Hospital, Stockholm, Sweden
e-mail: Paul.Hjemdahl@ki.se

M. Burnier (ed.), *Drug Adherence in Hypertension and Cardiovascular Protection*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-76593-8_8

The introduction of invasive treatment by renal denervation (RNx) for patients with resistant hypertension has prompted the need for optimization of antihypertensive drug therapy [3] and exclusion of non-adherence as a modifiable cause behind persistently elevated blood pressures before subjecting them to the risks associated with RNx. The high cost of the intervention also underscores the need for not offering it to patients unnecessarily [5]. Pseudoresistance to antihypertensive treatment caused by poor adherence is not an acceptable indication for RNx. Before considering RNx in a presumably resistant hypertensive patient, the possibility to control the patient's blood pressure with a regimen consisting of at least three drugs from different classes at optimal dosages should be ruled out according to present consensus whether the clinical setting is a trial or routine care. Effective diuretic therapy (preferably with chlorthalidone) and spironolactone seem to be underused [3]. Adherence is of course of key importance in this context.

Long-term adherence to a complex treatment regimen is notoriously difficult to document. Interviews, pharmacy claims, and electronic pill boxes are tools that yield some information but neither of them actually proves that the drugs are taken as prescribed. Self-reports of adherence (using the eight-item Morisky Medication Adherence Scale) were less likely to identify important non-adherence than pharmacy claims [6]. The latter provide valuable information on persistence but are less precise regarding drug-taking behavior [2]. Screening of the prescribed drugs or their metabolites in serum/plasma or urine has therefore evolved as an "objective" method for verifying adherence, especially in the context of RNx [2, 5, 7]. However, what is the robustness of a negative result (drug levels missing or too low) and what is the positive predictive value of finding all drugs in the sample? Furthermore, ethical issues need consideration and these may also influence the meaningfulness of the testing.

8.1 Drug/Metabolite Monitoring

Finding drug/metabolite levels compatible with intake of appropriate dosages of the drugs despite persistently elevated blood pressures supports the contention that there is resistance to treatment but does not prove good therapeutic coverage since this test provides "snap shot" information which may not be representative of the persons general adherence. Absence of any or all of the analytes sought in the sample would argue for poor adherence as a causative factor behind the "resistant" hypertension. Findings of low levels of the drug/metabolite are difficult to interpret due to interindividual variations, for many reasons, in pharmacokinetics and pharmacodynamics (PK/PD) of the drugs measured. The detection limits (sensitivities of the assays) are important and the time courses for excretion of the drugs or their metabolite(s) should preferably be known for different dosages and in patients with different levels of renal function. This underlying knowledge is needed for correct interpretation of test results.

The "time window" that the drug/metabolite analysis covers is obviously an important issue. This is for most antihypertensive drugs rather short—probably only

a couple of days depending on the drug/metabolite in question, its excretion pattern in the patient (which can vary), and the sensitivity of the assay. However, it can also be very long, as for amlodipine, and result in false positive results [2]. In addition, it is very difficult, if not impossible, to translate urinary drug levels into (therapeutic?) plasma levels. In drugs of abuse testing urine samples are preferred (although the samples can be adulterated to hide drug intake) since measurable levels persist longer in urine than in blood. Is urine or blood (plasma or serum?) the best matrix for the qualitative or (semi-)quantitative monitoring of antihypertensive drugs? What are the detection times in the matrix chosen and their confidence limits for the drugs tested, taking both the dosing and the interindividual variability in PK/PD into consideration? When is it reasonable to assume that the concentration measured is compatible with drug intake as prescribed? The analytical challenge will probably be greater with measurements in blood but such levels would be easier to interpret in terms of PK/PD. Perhaps a biomarker is preferable to drug analysis, if possible [2]? Regardless, interpretation of the findings should rest on basic knowledge which presently does not seem to be adequate.

When monitoring intake by drug/metabolite analyses, the time windows for most drugs will be rather short and the analysis will provide information of a "snap shot" nature rather than prove that the patient is adherent in the therapeutic sense. The "tooth brush" effect, i.e., taking the prescribed treatment before a visit to the doctor, is a well-known phenomenon which cannot be excluded with assays that measure recent drug intake only, and this will result in false positive results. Long-term information could be obtained by repeated measurements, but the tooth brush effect will probably be encouraged upon repeated monitoring even if this was not found to be a problem with one repeated measurement during routine care in a specialist clinic not focusing on "resistant" patients [8]. The best method for bioanalytical documentation of long-term adherence and therapeutic coverage would be to measure drug/metabolite levels in hair, which could cover a time frame of months, but I do not know if that is feasible.

8.2 Ethical Issues and Their Methodological Consequences

How and when should the patient be informed about the drug testing? Informed consent is mandatory whenever this is possible in a research project [9]. Should this not be the case also in routine health care? Using a sample for reasons other than those disclosed to the patient is unethical and confrontation of patients with unfavorable test results without previous information will no doubt endanger the patient's trust in the doctor responsible for clandestine testing and, in the worst case, perhaps even of health care in general. A false negative result—wrongly accusing the patient of not adhering—would be disastrous. If informed consent is obtained, when should this be? After sampling but before the analysis? Or before the sampling? In the former case, the patient may feel that it is difficult to withdraw consent when the sample has already been taken. The fairest way to treat the patient is to be honest about the testing but how should the patient who refuses testing then be treated?

In the study by Hamdidouche et al., written informed consent was obtained before sampling and no patient declined testing either on the first or the second occasion [8]. In studies of evaluating "resistant" hypertensive patients for RNx, the patients were unaware of the testing in [5] and procedures for information are not mentioned (probably absent) in [7]. In the study by Jung et al. [5], 50% of the patients were non-adherent or poorly adherent and 87.5% of them admitted poor adherence when confronted with test results which were stated to be "crucial information for the physician, allowing rational therapeutic decisions based on a measured parameter." In the study by Patel et al. [7], the finding of biochemical non-adherence led to exclusion of 8 out of 24 patients remaining in the diagnostic pathway for RNx after further blood pressure evaluation and questions regarding adherence. Hopefully, these "objective" tests excluded patients for whom RNx really was inappropriate and, hopefully, the procedures used led to improved adherence and increased therapeutic efficacy of the medications in these cases.

Regardless of the timing of the information, the possibility to obtain samples from unprepared patients will most likely disappear after the first sampling. Most patients with "resistant" hypertension due to poor adherence will probably anticipate renewed testing and take their drugs before future visits to avoid negative test results. Thus, repeated monitoring may yield erroneous results but patients are probably only given one chance in the workup for RNx.

8.3 Ethical Analysis and Conclusions

Benefits should be weighed against risks in health care as in research involving human subjects [9]. The value of monitoring adherence by drug/metabolite analyses is limited for both analytical reasons (detection periods and precision) and ethical reasons related to information and consent.

When evaluating patients for possible RNx, the benefit of biochemical monitoring is access to an "objective" measure of adherence but the value of this (with false positives and false negatives as outlined above) is limited. The risks are several and at least equally important. Generally, adherent persons may be rejected due to forgetfulness to take pills on the occasion of testing or due to methodological problems with the test. Non-adherent persons may pass the test due to the tooth brush effect or long persistence of drug levels despite poor adherence. These possibilities of faulty test results reduce the value of biochemical monitoring. Thus, the questionable robustness of the testing and the "snap shot" nature of the information obtained weigh against a favorable benefit/risk evaluation. Furthermore, issues related to information and consent may infringe on the autonomy and integrity of the patient.

Information and consent are key ethical issues. If the testing is performed without informed consent or even information, it is unacceptable from the patients' point of view. This way of handling the problem should be seriously reconsidered if the testing is performed to include or exclude individual patients from an RNx program but it may be acceptable if it is performed for research reasons and the results do not infringe on the integrity of individual participants. Ethical approval which waives

the need for information should be obtained for such studies. If the testing is performed in routine care, this should be preceded by informed consent and be part of an effort to increase adherence and obtain better therapeutic results.

Thus, both methodological and ethical aspects must be weighed into decisions to employ biochemical monitoring of antihypertensive treatment. Misuse of the technique may be counterproductive if it damages the patient–doctor relationship and the patients' trust in health care procedures. Used correctly biochemical monitoring may contribute to but not solve problems with the assessment of adherence.

What are then the alternatives? The key to good adherence and long-term persistence in a patient with hypertension lies in convincing the patient that taking the treatment as prescribed is in his/her best interest. The patient could become his/her own doctor and monitor the therapy with home blood pressure measurements. Electronic devices such as the MEMS monitor can be helpful for pedagogical purposes and pill boxes that remind the patient or a Dosette with dispensed medicines can help the patient remember to take the drugs. A simple way to assess persistence is to monitor pharmacy claims but this also has its problems and limitations. Patients may claim prescriptions without taking the medications, especially if they have previously been confronted with failures to claim prescriptions for drugs they do not want to take. How does one integrate a dialogue regarding pharmacy claims in the care of the patient in a constructive manner to improve therapeutic efficacy without infringing on the patients integrity? Repressive measures such as witnessed drug intake or biochemical monitoring of drug intake without informed consent should be handled with great care and preferably be avoided. Most importantly, the doctor should recognize the limited value of "snap shot" testing, especially if it is performed repeatedly, and respect the integrity and autonomy of the patient.

References

1. Vrijens B, Antoniu S, Burnier M, de la Sierra A, Volpe M. Current situation of medication adherence in hypertension. Front Pharmacol. 2017;8:100.
2. Hamdidouche I, Jullien V, Boutouyrie P, et al. Drug adherence in hypertension: from methodological issues to cardiovascular outcomes. J Hypertens. 2017;35:1135–44.
3. Cai A, Calhoun DA. Resistant hypertension—an update of experimental and clinical findings. Hypertension. 2017;70:5–9.
4. Albarquoni L, Doust J, Glasziou P. Patient preferences for cardiovascular preventive medication: a systematic review. Heart. 2017;103(20):1578–86. https://doi.org/10.1136/heartjnl-2017-311244. Online publ. May 13.
5. Jung O, Gechter JL, Wunder C, et al. Resistant hypertension? Assessment of adherence by toxicological urine analysis. J Hypertens. 2013;31:766–74.
6. Kroussel-Wood M, Holt E, Joyce C, et al. Differences in cardiovascular disease risk when antihypertensive medication adherence is assessed by pharmacy fill versus self-report: the Cohort Study of Medication Adherence among Older Adults (CoSMO). J Hypertens. 2015;33:412–20.
7. Patel P, Gupta PJC, White CMJ, et al. Screening for non-adherence to antihypertensive treatment as a part of the diagnostic pathway to renal denervation. J Hum Hypertens. 2016;30:368–73.

8. Hamdidouche I, Jullien V, Boutouyrie P, et al. Routine urinary detection of antihypertensive drugs for systematic evaluation of adherence to treatment in hypertensive patients. J Hypertens. 2017;35(9):1891–8.
9. World Medical Association. World Medical Association Declaration of Helsinki—ethical principles for medical research involving human subjects. JAMA. 2013;310:2191–4.

Part II

Risk Factors for Non-adherence

Determinants and Barriers to Adherence in Hypertension

9

Valentina Forni Ogna and Michel Burnier

9.1 Introduction

Hypertension remains a leading cause of cardiovascular (CV) morbidity and mortality in the world [1], despite the growing evidence form clinical trials proving the effectiveness of antihypertensive therapy (AHT) in controlling blood pressure (BP) and reducing the CV risk [2]. Nevertheless, in real life, a noticeable proportion of hypertensive individuals appears to be unaware of the risk or, if aware, does not undergo therapy [3, 4]. Furthermore, target BP levels are often not achieved in treated hypertensive patients [5, 6]. In the last guidelines of the European Society of Hypertension [2], patient low adherence to treatment is considered to be one of the three main causes of the low rate of BP control, besides physician inertia and deficiencies of health care systems. In real life situations, the percentage of hypertensive patients that can be considered as "good compliers" is highly variable depending on the methodology used to assess it and therefore ranges between 20 and 80% [7]. Even in clinical studies, median persistence with AHT is low, about 50–60% at 1 year [8].

The published literature identified hundreds of determinants of non-adherence to long-term therapies [9]. One important aspect to consider in order to understand the phenomenon of non-adherence to AHT is that hypertension is a lifelong, chronic, often asymptomatic condition. In its therapeutic way consisting of a daily therapy for years to treat a silent condition, the patient may be faced with several heterogeneous barriers, intervening at different times of life, affecting its capacity to initiate, implement, or persist with physicians' prescriptions, and ultimately leading to its discontinuation [10] (Fig. 9.1).

V. F. Ogna (✉) • M. Burnier
Service of Nephrology and Hypertension, Department of Medicine, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland
e-mail: valentina.forni@chuv.ch; michel.burnier@chuv.ch

M. Burnier (ed.), *Drug Adherence in Hypertension and Cardiovascular Protection*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-76593-8_9

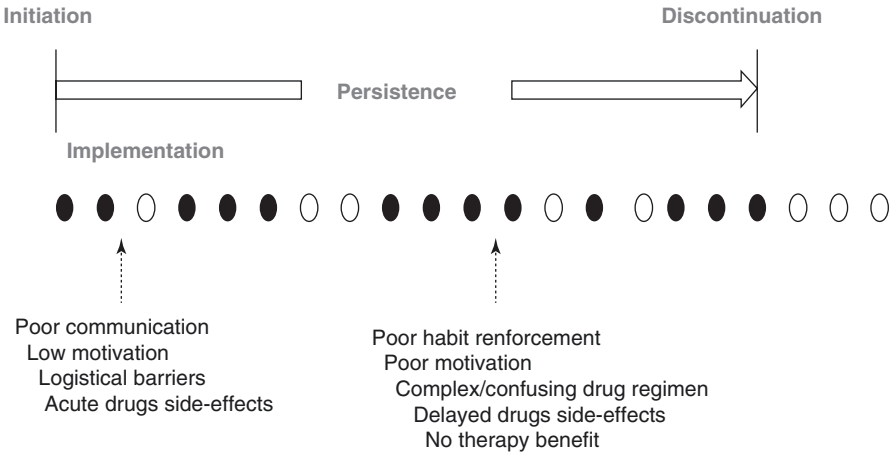


Fig. 9.1 Sequential barriers to adherence with antihypertensive therapy

Table 9.1 The WHO interacting dimensions affecting adherence to long-term therapies

1.	Patient's understanding and perception
2.	Demographic factors (gender, age, and education)
3.	Health care provider's mode of delivering treatment
4.	Relationships between patients and health care professionals
5.	Health systems influences
6.	Therapy-related factors

This schema is not an exhaustive list of all possible barriers to adherence, but it shows how obstacles may intervene in different phases of the adherence process (from initiation, to implementation, to persistence).

In 2003 [11], the World Health Organization (WHO) published a detailed report identifying five interacting dimensions affecting adherence to long-term therapies as illustrated in Table 9.1.

In this chapter, we will review the determinants and barriers to adherence in hypertension utilizing the WHO Multidimensional Adherence Model classification (Fig. 9.2), showing in which phase of the adherence process they intervene. We will review how these barriers may complicate the therapeutic history of a hypertensive patient as illustrated in the clinical case described below.

9.2 Clinical Case

Mr. H. is a 72-year-old man of Caucasian origin, married and father of two adult children, retired for 7 years. He has a 50 years history of poorly controlled essential hypertension. The hypertension diagnosis was done during a military check-up at age 20. Thereafter, he was employed by a car dealer. He was always considered as

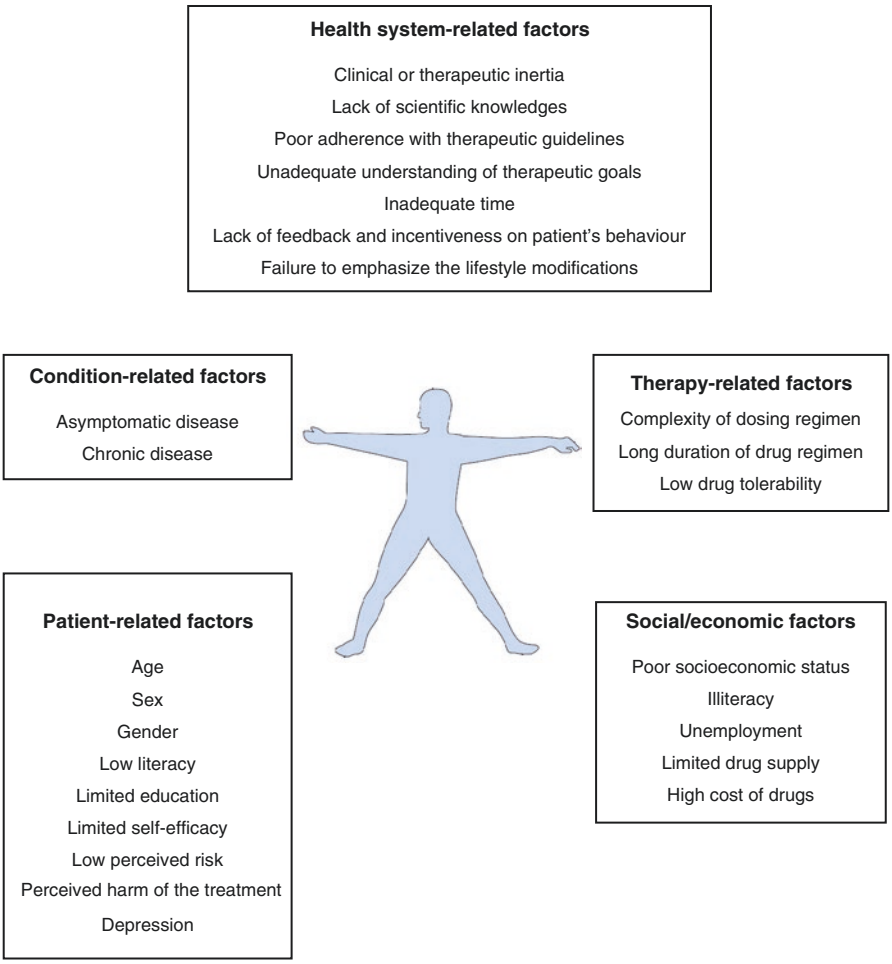


Fig. 9.2 Barriers to antihypertensive medications adherence according to the World Health Organization Domains (Open access) [11]

in good health and was never feeling sick. His father had also high BP but was older than 80 years and without any complication. So our patient did not listen to the military doctor recommending looking for a family doctor and for the next 10 years he forgot about his high BP. At age 30, he sought medical advice for chronic lumbar pain, and his BP was measured at 175/105 mmHg. The patient was smoking and became overweight. The general practitioner was concerned and addressed Mr. H. to a cardiologist, who prescribed the first pharmacological therapy associating propranolol 80 mg twice daily, and chlortalidone 25 mg once daily. In addition, he urged the patient to lose weight and to do more physical activity and discouraged him from taking non-steroidal anti-inflammatory drugs (NSAID) to treat his lumbar pains. Mr. H. did not really understand why his BP values stressed doctors but

thought it was better to follow the prescriptions. Almost immediately he noticed urinary urgencies several times during day and night. A colleague told him this was an adverse effect of diuretics and so he decided to stop chlortalidone, with prompt resolution of the annoying problem. He did not feel any negative effect of propranolol, so he continued the therapy, forgetting occasionally the evening dose. At the same time, his back pain was more and more intense and he could not deprive himself from the NSAIDs. In his professional life, he was limited because of the pain and he started to be depressed.

BP values were always too high when measured by his physician, and olmesartan 40 mg once a day was added to his regimen. Mr. H. accepted, without telling him he had stopped chlortalidone and was continuing NSAIDs. He continued not to understand the fears of his primary care physician and the potential consequences of his uncontrolled hypertension. After all, he did not feel high BP and his father had survived without damages to decades of hypertension. Furthermore, he could not feel any benefit from his treatment or rather he had to suffer the adverse effects and he sometimes worried about becoming too dependent on these pills. His wife was convinced that the problem was too much stress; and thought that BP would normalize if his husband could reduce the workload. She asked the help of a naturopath, who prescribed him some herbal medicines and informed the patient that propranolol could provoke sexual dysfunction. Mr. H's motivation to take drugs and its trust in physicians drastically collapsed. For 5 years, he did not seek medical advice, until he was hospitalized in emergency for unstable angina pectoris and had a coronary revascularisation. His BP was very high. The day of hospital discharge, the young fellow of cardiology delivered him a recipe with seven medicaments listed (five of which for BP control) and counselled him to suppress salt and fats from his diet, to stop smoking and to reduce his alcohol consumption.

9.3 Patient's Understanding and Perception of Hypertension

What the patient understands and believes is closely associated with the level of adherence to therapy, but these factors have the characteristic to change with time and to be modifiable positively or negatively. Initially, the diagnosis of hypertension often triggers a strong denial reaction and generates considerable socioeconomic threats that may further inhibit the patient from accepting the diagnosis and dealing with a therapeutic strategy. Like in the case of Mr. H., many patients are found to be hypertensive when they are in their 30s and early 40s years, when the threat of a loss of vigour and energy is insidiously beginning.

In the history of Mr. H., we can identify some important psychological barriers to the adherence to therapy: **lack of understanding of the disease and consequently low perceived risk of the diseases consequences** [12–14]. Mr. H. is largely unaware of the nature of hypertension and of its possible causes. He ignores the potential clinical consequences of an inappropriate BP control based on his father's experience. Therefore, he does not understand the therapeutic needs and

why his physicians are so concerned. In this patient, one can also note the **perceived ineffectiveness and harm of treatment, the lack of self-efficacy, and lack of involvement in the treatment decision-making process** [15, 16]. Patients with such characteristics are less likely to take their medication, to adopt healthy lifestyle changes, or to contact their physician if their BP is outside the desired range [17].

Frequently, patients perceive hypertension as an acute intermittent symptomatic condition and not as a chronic asymptomatic disease needing a long-term pharmacotherapy [18, 19]. Mr. H.'s wife seems to adhere to the "stress model" of hypertension and beliefs that hypertension will resolve once stress is reduced. This is the common error of confounding nervous tension with hypertension. The notion of hypertension as a "simple anomaly" and not a disease that is directly related to heart disease and stroke was a commonly cited explanation for not taking AHT in an observational study exploring uncontrolled hypertension among French patients [20]. Health beliefs are strongly influenced by the social context and personal experiences of the patient: patients who experienced hypertension-related symptoms or had family members with a history of hypertensive disease and experienced hypertension-related complications are more likely to view hypertension as a serious condition, and are more likely to describe a willingness to make lifestyle changes [21]. This is not the case of Mr. H. who is asymptomatic and has been confronted with a hypertensive father living over 80 years without any hypertension-related complication. Results suggest that the objective severity of patients' disease conditions, and their awareness of this severity, can predict their adherence [22]. The issue of "Beliefs and adherence" will be discussed in more depth in Chap. 10.

9.4 Comorbidities

Comorbidities may represent a serious obstacle to the adherence process. For example, mental health status (e.g. stress, depression, anxiety), cognitive dysfunction in elderly and substance abuse have constantly been proved to reduce adherence [23]. Some elements of our patient's history could indicate the presence of an unsolved psychological overload: he feels stressed, he cannot handle the workload, he shows no interest and initiative to take care of his health problems.

A meta-analysis exploring the association between psychiatric illness and medical adherence [24], showed that depressed patients had a three times higher likelihood of being non-adherent to medical prescriptions, while the association between anxiety and non-adherence was variable.

9.5 Demographic Factors

Patient demographic characteristics (e.g. gender, age, marital status) have not been consistently related to poor adherence [23]. This can partly explain why health care providers are ineffective in predicting adherence rate in their patients [9].

9.5.1 Gender

It is generally reported that women are more adherent to therapy than men. Yet, this assumption is not always supported by data. A systemic meta-analysis published in 2017, including 28 studies and 12,603 subjects from 15 countries in the four continents, analysed the demographic determinants of adherence to AHT using the Morisky medication adherence scale-8 (MMAS-8) [25]. The findings about sex differences revealed that although a higher percentage (54% vs. 46.2%) of non-adherence to medications was noticed in women ($P < 0.001$), the risk of non-adherence was 1.3 time higher in men, with a relative risk of 0.883 (95% CI = 0.76–1.02, $P = 0.104$). These figures were higher than those published by Holt et al. [26] who focussed on elderly hypertensive patients assessed by MMAS-8. In this study, 15% of women vs. 13.1% of men had low adherence scores. In a recent retrospective study [27], analysing non-adherence to AHT using high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS)-based assay in the UK and Czech general population, the odds of the overall non-adherence were 65% and 55% higher in women than in men in the UK and Czech populations, respectively. No difference was noticed between men and women in the elderly hypertensive population of the CoSMO study [28].

Nevertheless, sex seems to condition the influence of some somatic, psychosocial, and behavioural factors on medication adherence. For example, depression has been identified as an important correlate of low adherence, particularly among older women [26]. Among men, higher body mass index (BMI $\geq$25 kg/m^2) has been associated with lower medication adherence scores, even after adjusting for depression and stress. A possible explanation is that patients who do not take their medications may also be less likely to exercise and follow dietary regimens [26]. In a recent study conducted on French patients with uncontrolled hypertension, obesity and a history of stroke were associated with poor drug adherence in men, whereas in women the most common factors were past or current smoking or infrequent contact with their family doctor [20].

Sexual dysfunction acts as a barrier to AHT adherence in men, but not women. Sexual dysfunction is highly prevalent in hypertensive adults [29] and could stem from both the physiological impact of hypertension itself, and/or side effects of the pharmacologic regimen [30]. Earlier work revealed that patients who perceive that their medication therapy is linked with their sexual problems may have sustained adherence problems [31]. A 2005 retrospective analysis of prescription claims showed that when erectile dysfunction in men was treated with sildenafil, adherence to hypertensive treatments subsequently improved [32]. When prescribing a pharmacological regimen to a sexually active patient, like Mr. H., doctors should consider the risk of interfering with his sexual performance and talk about it. In our patient, the prescription of two medication classes susceptible to induce sexual dysfunction (the non-selective beta-blocker propranolol and the thiazide-like diuretic chlortalidone) was a risky choice. Identifying and addressing any perceived sexual side effects of AHT might successfully improve adherence in men.

9.5.2 Age

Concerning the impact of age, studies of non-adherence to AHT have been conducted mostly among middle-aged and elderly patients, not enabling to compare the extreme age effect [33–36]. Nevertheless, studies including subjects from a wider age range showed that younger age is a strong predictor of poor adherence. For example, in an analysis of data from NHANES 1999–2002, subjects <30 years old were 12 times more likely to be non-adherent than those ≥50 years old, independent of other risk factors [37]. The observed age effect was of the same direction but stronger than the effect reported in a previous study [38]. It can be speculated that youngs are more reluctant to accept the chronic administration of pills interfering with their life activity to treat an asymptomatic condition. In the UK and Czech general population-based retrospective trial [27] exploring non-adherence using a HPLC-MS/MS-based assay, age showed an inverse association with non-adherence: every 10-year increase in age was associated with just >30% reduction in the odds of non-adherence. Hypertensive elderly individuals may face specific challenges, including multiple medications with frequent dosing, and potentially decreased dexterity or cognitive function. Elderly patients seem particularly sensitive to the phenomenon of cost-related underuse of medications, which is associated with health care coverage factors (e.g. increasing out-of-pocket costs, inadequate prescription coverage), as well as with the quality of the physician–patient relationship [39, 40]. Results from a US national survey of Medicare Beneficiaries aged ≥65 years showed that 39% of seniors who reported cost-related non-adherence had failed to discuss cost-related non-adherence issues during the visit with their physician [41]. Another study showed that patients who give lower priority to discussing their hypertension-related concerns with the physician are significantly more likely to be non-adherent to their medication [42].

Elderly patients are faced to potentially destabilizing life events, like hospitalisations and retirement. The periods following the hospital discharge [43] and retirement [44] were both found to be characterized by a high rate of poor adherence among elderly. Of note, in elderly patients, cognitive dysfunction may result in both an underuse and an overuse of prescribed medications which may lead to clinical complications.

9.5.3 Race

Subjects of different ethnic backgrounds have unique adherence issues associated with several factors such as beliefs, tolerance of side effects and expectations. The meta-analysis of non-adherence to AHT published in 2017 [25] reported a sensitivity analysis stratified for different continents. This analysis showed a significant non-adherence level in hypertensive patients with major regional differences. Thus, studies carried out in Africa showed a higher percentage of poor adherence levels (62.4%) than Asians (43.5%), Europeans (36.6%), and Americans (36.6%). There is

strong consensus that medication low adherence rates are higher among patients of African or African-American origin, with respect to whites [45]. The African race has been shown to have a major influence on hypertension prevalence, hypertension awareness, hypertension-associated CV complications [46], and on the response to AHT [47]. Interestingly, it seems also that in the United States, physicians demonstrate less empathy, concern, courtesy, information giving, and nonverbal attention when caring African-American patients [48].

9.5.4 Socioeconomic Status

Conventional wisdom suggests that poor socioeconomic status is a strong predictor of medication non-adherence, through its effect on access to medications, health literacy, and medication knowledge [49]. In reality, current evidence about the association between socioeconomic status and AHT adherence is poor, mostly because of strong limitations in the assessment of socioeconomic status in published research [50].

9.6 Health Care Providers' Mode of Delivering Treatment and Relationships Between Patients and Health Care Professionals

The health care providers share with the patient the responsibility for a good adherence: positive relationship, good quality of communication, positive interactions, empathic, non-judgemental attitude, and ready availability are some health care provider's characteristics having been shown to positively impact adherence [51]. In the contrary, **inadequate time dedicated to the patients, lack of incentives and positive feedbacks on patient's behaviour,** and **failure to encourage the lifestyle modifications** necessary in the management of the chronic disease have detrimental effects on adherence [52]. Analysing the patient–doctors relationship in Mr. H.'s history, we are impressed by the poor quality of communication of the various physicians in charge. Doctors provide scientific arguments on the possible consequences of not adequately treating hypertension and these latter are projected on a "disastrous future". However Mr. H.'s unexpressed thoughts are focussed on the actual paucity of symptoms and on the fear for adverse effects. The young fellow intervening at the end of the clinical case acts according to evidence-based medicine without considering the past experiences of his patient. This attitude has a little chance of success.

Other major physician-related barriers concern the scientific domain, including: **lack of scientific knowledge, poor adherence with therapeutic guidelines** [53]**, inadequate understanding of therapeutic goals** [54]**, and clinical or therapeutic inertia** [55].

In 2001, Phillips introduced the concept of "clinical inertia" [56] to describe the phenomenon of the health care providers who do not initiate or intensify the therapy

appropriately when therapeutic goals are not reached: "***recognition of the problem, but failure to act***". Since then, more reasons for therapeutic inertia have been identified: overestimation of care, soft reasons (i.e. "improving control", "target almost reached"), lack of training and organization at "treating to target", clinical uncertainty (defined as the feeling of the physician that the numbers might not be reliable and therefore the patient might not be hypertensive) [57] and competing demands (the effect of unrelated comorbid conditions on hypertension management) [58]. In 2006, Okonofua [57] introduced the terms of "therapeutic inertia" and since then, the two terms "clinical inertia" and "therapeutic inertia" have been used indistinctly. Inertia has been shown to significantly contribute to suboptimal BP control rates in treated patients [59, 60].

9.7 Health Systems Influences

Patients and health care providers are influenced by their national health care system, which may affect the access to therapy through the choice of **health care delivery** (e.g. access to primary care, availability of self-management support), **health care financing** (e.g. health insurance, prescription drug coverage) and **health care strategies** to promote adherence. As all chronic diseases, hypertension management requires a long-term reliable supply of medications, at an affordable price. This can be problematic in low income countries, where drugs often have to be bought out-of-pocket. A recent review [61] analysed the influence of medication payment schemes on patients' medication adherence: copayment or out-of-pocket expenditure, drug coverage or insurance benefit, prescription benefit coverage limits or prescription cap, and free of charge or fully subsidized were found to affect drug adherence. The higher out-of-pocket expenditure or copayment borne by patients influenced patients' medication adherence depending on (1) the amount of out-of-pocket money spent for medications, (2) the perceived financial burden of medication, and (3) type of patients and diseases such as young-aged and chronic diseases. A Commonwealth survey published in 2009 estimated that cost-related medication non-adherence ranged from 3% in the Netherlands to 43% in the United States [62]. A multi-national cross-sectional European survey [63] found significant differences in self-reported non-adherence to AHT across the sampled European countries (from 34% in Austria to 70% in Hungary). The main finding is that differences are not exclusively explained by the country effect, but also by heterogeneities of populations in cost-related factors, low perceived self-efficacy, and high perceived barriers. The findings of a study conducted in the United Kingdom including hypertensive patients suggested that patients may not feel comfortable discussing cost issues with their doctors, considering that financial problems do not concern doctors [64]. However, according to the principle of concordance, doctor and patients should share all concerns about medication, including the issues of costs and affordability in order to reach a therapeutic alliance. Health systems-related strategies for improving adherence and access to drugs are discussed in Part IV of this book.

9.8 Complexity of Antihypertensive Drug Regimens

The best investigated determinants of adherence are those related to the pharmacotherapy itself and can be categorized in four domains: drug tolerability, drug costs, treatment duration, and regimen complexity. The subject of drug therapy returns frequently in the speech of Mr. H., with a very negative connotation.

The role of **drug tolerability** in adherence to AHT is a topic for debate. Many investigators argue that the fewer the drugs side effects, the better the adherence [65–67]. Patients with newly diagnosed hypertension are good candidates to analyse the impact of acute side effects on adherence since suboptimal daily implementation of the newly prescribed AHT regimen has been demonstrated to be one of the most common factors for poor persistence [8]. Observational studies focussing on incident patients have shown that initial treatment with angiotensin-converting enzyme inhibitors, angiotensin II antagonists, and calcium channel blockers favoured treatment persistence, when compared to diuretics and beta-blockers [34, 68–70]. In agreement with the "tolerability hypothesis" angiotensin II antagonists—a class known for its very good tolerability profile [71]—show the best persistence among all other AHT drug classes in newly treated patients [69, 72].

The "**tolerability hypothesis**" emerging from observational studies has been questioned by the results of some randomized controlled trials. Indeed, measures of quality of life in the Treatment of Mild Hypertension Study [73] were higher with chlorthalidone and acebutolol than with enalapril, amlodipine, and doxazosin. Pooled results from head-to-head randomized controlled trials that recorded discontinuation of medications due to adverse events have demonstrated that significantly fewer patients discontinued treatment with thiazide diuretics, than with beta-blockers and alpha-adrenergic blockers [74]. The unsolved question is if adherence results of traditional clinical trials are suitable to interpret drug adherence in the today world, since some aspects of adherence, like initiation and persistence, are better in clinical trials than in clinical practice [75]. Moreover, the tolerability profile of newer drugs has improved considerably.

Once correctly implemented, the therapy should be continued for many years. A multi-national cross-sectional European survey [76] analysed the determinants of non-persistence to AHT. The main findings were that patients were less likely to continue with their medications if the dose frequency or the probability of adverse effects were high, while they were more likely to continue when the probability of treatment benefits increased.

The impact of **medication regimen factors** on adherence to some chronic diseases, among which hypertension, has been resumed in a literature review published in 2008 [77]. Three of the seven included studies [78–80] used electronic monitoring to measure adherence. To summarize their findings, there is strong evidence that once-daily dosing results in a superior adherence compared to multiple daily

dosing, but it is less clear whether there is a decrement in adherence for each additional dose per day [78–82].

In a study including more than 8000 adults initiating simultaneous AHT and lipid-lowering treatment, Chapman [83] observed that patients taking no other medications were almost twice as likely to be adherent as those taking six or more medications.

In contrast, George [84] found that a higher number of concurrent medications predicted good adherence in a study of 350 clinic patients with congestive heart failure and suggested that taking more medications may require a higher level of attention and therefore improve adherence. In the previously described retrospective analysis using biochemistry to assess non-adherence, Gupta [27] found that, on average, every increase in the number of prescribed drugs was associated with 85% and 77% increase in the odds of the non-adherence in the UK and Czech populations, respectively. Based on the existing evidence, it appears that the number of concurrent medications may contribute to adherence as well as to non-adherence depending on the clinical situation.

One frequently proposed strategy to simplify the treatment regimens is to use single-pill combinations, containing long-acting substances [85]. The use of single-pill combinations has the advantage to enable once-daily dosing and to reduce the pill burden. It has been associated with a higher adherence and an improved BP normalization ratio compared with free combinations [86–89], but it also has some drawbacks. Indeed, if the patient omits to take one pill, he actually misses more pharmacological agents simultaneously, increasing the risk of rebound effects. Paradoxically, the twice-daily regimen could ensure a better continuity of drug exposure than does the once-daily regimen in patients with adherence problems although the twice-daily regimen creates twice as many opportunities for missing a dose. This is the basis of the paradox of the "twice-daily advantage": better drug efficacy despite a higher percentage of prescribed doses omitted [90]. Thus, the once-daily treatment should not be a dogma, particularly in difficult-to-treat hypertensive patients.

Conclusions

The therapeutic management of hypertensive patients implies a lifelong treatment with various medications which is sprinkled with pitfalls and obstacles limiting the acute as well as the long-term adherence to medications. Barriers can occur at beginning of the path, hindering correct implementation of the therapy, or can manifest after some months or even years, threatening persistence. Obstacles may be of different nature, varying from patient's and health care professionals' peculiarities, to socioeconomic context and therapy's characteristics. A comprehensive understanding of adherence barriers, including all dimensions that can affect potential modifiable individual attitudes, is essential to design effective interventions to enhance medication adherence and to evaluate the impact of these interventions on adherence rates and ultimately patient outcome.

References

1. Ezzati M, Lopez AD, Rodgers A, Vander Hoorn S, Murray CJ, Comparative Risk Assessment Collaborating Group. Selected major risk factors and global and regional burden of disease. Lancet. 2002;360(9343):1347–60.
2. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2013;31(7):1281–357.
3. Burt VL, Cutler JA, Higgins M, Horan MJ, Labarthe D, Whelton P, et al. Trends in the prevalence, awareness, treatment, and control of hypertension in the adult US population. Data from the health examination surveys, 1960 to 1991. Hypertension. 1995;26(1):60–9.
4. Reiner Z, Sonicki Z, Tedeschi-Reiner E. Physicians' perception, knowledge and awareness of cardiovascular risk factors and adherence to prevention guidelines: the PERCRO-DOC survey. Atherosclerosis. 2010;213(2):598–603.
5. Amar J, Chamontin B, Genes N, Cantet C, Salvador M, Cambou JP. Why is hypertension so frequently uncontrolled in secondary prevention? J Hypertens. 2003;21(6):1199–205.
6. Mancia G, Ambrosioni E, Rosei EA, Leonetti G, Trimarco B, Volpe M, et al. Blood pressure control and risk of stroke in untreated and treated hypertensive patients screened from clinical practice: results of the ForLife study. J Hypertens. 2005;23(8):1575–81.
7. Costa FV. Compliance with antihypertensive treatment. Clin Exp Hypertens. 1996;18(3–4):463–72.
8. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. Br Med J. 2008;336(7653):1114–7.
9. Ascertaining barriers for compliance: policies for safe, effective and cost-effective use of medicines in Europe. 2012: 1–542 pp.
10. Rudd P. Clinicians and patients with hypertension: unsettled issues about compliance. Am Heart J. 1995;130(3 Pt 1):572–9.
11. World Health Organization. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization; 2003.
12. Wang PS, Bohn RL, Knight E, Glynn RJ, Mogun H, Avorn J. Noncompliance with antihypertensive medications: the impact of depressive symptoms and psychosocial factors. J Gen Intern Med. 2002;17(7):504–11.
13. Cummings KM, Kirscht JP, Binder LR, Godley AJ. Determinants of drug treatment maintenance among hypertensive persons in inner city Detroit. Public Health Rep. 1982;97(2):99–106.
14. Ryan AA. Medication compliance and older people: a review of the literature. Int J Nurs Stud. 1999;36(2):153–62.
15. Ogedegbe G, Mancuso CA, Allegrante JP, Charlson ME. Development and evaluation of a medication adherence self-efficacy scale in hypertensive African-American patients. J Clin Epidemiol. 2003;56(6):520–9.
16. Haynes RB, McDonald HP, Garg AX. Helping patients follow prescribed treatment: clinical applications. JAMA. 2002;288(22):2880–3.
17. Knight EL, Bohn RL, Wang PS, Glynn RJ, Mogun H, Avorn J. Predictors of uncontrolled hypertension in ambulatory patients. Hypertension. 2001;38(4):809–14.
18. Meyer D, Leventhal H, Gutmann M. Common-sense models of illness: the example of hypertension. Health Psychol. 1985;4(2):115–35.
19. Sharkness CM, Snow DA. The patient's view of hypertension and compliance. Am J Prev Med. 1992;8(3):141–6.
20. Reach G, Guedj-Meynier D, Darne B, Herpin D. [Factors associated with medication nonadherence in uncontrolled hypertensive males and females: ODACE study]. Annales de cardiologie et d'angeiologie. 2015;64(3):222–6.

21. Boutin-Foster C, Ogedegbe G, Ravenell JE, Robbins L, Charlson ME. Ascribing meaning to hypertension: a qualitative study among African Americans with uncontrolled hypertension. Ethn Dis. 2007;17(1):29–34.
22. DiMatteo MR, Haskard KB, Williams SL. Health beliefs, disease severity, and patient adherence: a meta-analysis. Med Care. 2007;45(6):521–8.
23. DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. Med Care. 2004;42(3):200–9.
24. DiMatteo MR, Lepper HS, Croghan TW. Depression is a risk factor for noncompliance with medical treatment: meta-analysis of the effects of anxiety and depression on patient adherence. Arch Intern Med. 2000;160(14):2101–7.
25. Abegaz TM, Shehab A, Gebreyohannes EA, Bhagavathula AS, Elnour AA. Nonadherence to antihypertensive drugs: a systematic review and meta-analysis. Medicine. 2017;96(4):e5641.
26. Holt E, Joyce C, Dornelles A, Morisky D, Webber LS, Muntner P, et al. Sex differences in barriers to antihypertensive medication adherence: findings from the cohort study of medication adherence among older adults. J Am Geriatr Soc. 2013;61(4):558–64.
27. Gupta P, Patel P, Strauch B, Lai FY, Akbarov A, Maresova V, et al. Risk factors for nonadherence to antihypertensive treatment. Hypertension. 2017;69(6):1113–20.
28. Coons SJ, Sheahan SL, Martin SS, Hendricks J, Robbins CA, Johnson JA. Predictors of medication noncompliance in a sample of older adults. Clin Ther. 1994;16(1):110–7.
29. Martin-Morales A, Sanchez-Cruz JJ, Saenz de Tejada I, Rodriguez-Vela L, Jimenez-Cruz JF, Burgos-Rodriguez R. Prevalence and independent risk factors for erectile dysfunction in Spain: results of the Epidemiologia de la Disfuncion Erectil Masculina Study. J Urol. 2001;166(2):569–74; discussion 74–5.
30. Grimm RH Jr, Grandits GA, Prineas RJ, McDonald RH, Lewis CE, Flack JM, et al. Long-term effects on sexual function of five antihypertensive drugs and nutritional hygienic treatment in hypertensive men and women. Treatment of Mild Hypertension Study (TOMHS). Hypertension. 1997;29(1 Pt 1):8–14.
31. Manolis A, Doumas M. Sexual dysfunction: the 'prima ballerina' of hypertension-related quality-of-life complications. J Hypertens. 2008;26(11):2074–84.
32. McLaughlin T, Harnett J, Burhani S, Scott B. Evaluation of erectile dysfunction therapy in patients previously nonadherent to long-term medications: a retrospective analysis of prescription claims. Am J Ther. 2005;12(6):605–11.
33. Siegel D, Lopez J, Meier J. Antihypertensive medication adherence in the Department of Veterans Affairs. Am J Med. 2007;120(1):26–32.
34. Monane M, Bohn RL, Gurwitz JH, Glynn RJ, Levin R, Avorn J. The effects of initial drug choice and comorbidity on antihypertensive therapy compliance: results from a population-based study in the elderly. Am J Hypertens. 1997;10(7 Pt 1):697–704.
35. Monane M, Bohn RL, Gurwitz JH, Glynn RJ, Levin R, Avorn J. Compliance with antihypertensive therapy among elderly Medicaid enrollees: the roles of age, gender, and race. Am J Public Health. 1996;86(12):1805–8.
36. Perreault S, Lamarre D, Blais L, Dragomir A, Berbiche D, Lalonde L, et al. Persistence with treatment in newly treated middle-aged patients with essential hypertension. Ann Pharmacother. 2005;39(9):1401–8.
37. Bautista LE. Predictors of persistence with antihypertensive therapy: results from the NHANES. Am J Hypertens. 2008;21(2):183–8.
38. Caro JJ, Salas M, Speckman JL, Raggio G, Jackson JD. Persistence with treatment for hypertension in actual practice. CMAJ. 1999;160(1):31–7.
39. Piette JD, Heisler M, Wagner TH. Cost-related medication underuse among chronically ill adults: the treatments people forgo, how often, and who is at risk. Am J Public Health. 2004;94(10):1782–7.
40. Wilson IB, Rogers WH, Chang H, Safran DG. Cost-related skipping of medications and other treatments among Medicare beneficiaries between 1998 and 2000. Results of a national study. J Gen Intern Med. 2005;20(8):715–20.

41. Wilson IB, Schoen C, Neuman P, Strollo MK, Rogers WH, Chang H, et al. Physician-patient communication about prescription medication nonadherence: a 50-state study of America's seniors. J Gen Intern Med. 2007;22(1):6–12.
42. Turner BJ, Hollenbeak C, Weiner MG, Ten Have T, Roberts C. Barriers to adherence and hypertension control in a racially diverse representative sample of elderly primary care patients. Pharmacoepidemiol Drug Saf. 2009;18(8):672–81.
43. Gray SL, Mahoney JE, Blough DK. Medication adherence in elderly patients receiving home health services following hospital discharge. Ann Pharmacother. 2001;35(5):539–45.
44. Kivimaki M, Batty GD, Hamer M, Nabi H, Korhonen M, Huupponen R, et al. Influence of retirement on nonadherence to medication for hypertension and diabetes. CMAJ. 2013;185(17):E784–90.
45. Charles H, Good CB, Hanusa BH, Chang CC, Whittle J. Racial differences in adherence to cardiac medications. J Natl Med Assoc. 2003;95(1):17–27.
46. Lloyd-Jones D, Adams RJ, Brown TM, Carnethon M, Dai S, De Simone G, et al. Executive summary: heart disease and stroke statistics--2010 update: a report from the American Heart Association. Circulation. 2010;121(7):948–54.
47. Sehgal AR. Overlap between whites and blacks in response to antihypertensive drugs. Hypertension. 2004;43(3):566–72.
48. Orth JE, Stiles WB, Scherwitz L, Hennrikus D, Vallbona C. Patient exposition and provider explanation in routine interviews and hypertensive patients' blood pressure control. Health Psychol. 1987;6(1):29–42.
49. Briesacher BA, Gurwitz JH, Soumerai SB. Patients at-risk for cost-related medication nonadherence: a review of the literature. J Gen Intern Med. 2007;22(6):864–71.
50. Alsabbagh MH, Lemstra M, Eurich D, Lix LM, Wilson TW, Watson E, et al. Socioeconomic status and nonadherence to antihypertensive drugs: a systematic review and meta-analysis. Value Health. 2014;17(2):288–96.
51. Wright J, Lee C, Chambers G. Real-world effectiveness of antihypertensive drugs. Can Med Assoc J. 2000;162:190–1.
52. Hicks LS, Shaykevich S, Bates DW, Ayanian JZ. Determinants of racial/ethnic differences in blood pressure management among hypertensive patients. BMC Cardiovasc Disord. 2005;5(1):16.
53. Mehta SS, Wilcox CS, Schulman KA. Treatment of hypertension in patients with comorbidities: results from the study of hypertensive prescribing practices (SHyPP). Am J Hypertens. 1999;12(4 Pt 1):333–40.
54. Wang L. Physician-related barriers to hypertension management. Med Princ Pract. 2004;13(5):282–5.
55. Lebeau JP, Cadwallader JS, Aubin-Auger I, Mercier A, Pasquet T, Rusch E, et al. The concept and definition of therapeutic inertia in hypertension in primary care: a qualitative systematic review. BMC Fam Pract. 2014;15:130.
56. Phillips LS, Branch WT, Cook CB, Doyle JP, El-Kebbi IM, Gallina DL, et al. Clinical inertia. Ann Intern Med. 2001;135(9):825–34.
57. Okonofua EC, Simpson KN, Jesri A, Rehman SU, Durkalski VL, Egan BM. Therapeutic inertia is an impediment to achieving the Healthy People 2010 blood pressure control goals. Hypertension. 2006;47(3):345–51.
58. Turner BJ, Hollenbeak CS, Weiner M, Ten Have T, Tang SS. Effect of unrelated comorbid conditions on hypertension management. Ann Intern Med. 2008;148(8):578–86.
59. Rose AJ, Berlowitz DR, Orner MB, Kressin NR. Understanding uncontrolled hypertension: is it the patient or the provider? J Clin Hypertens. 2007;9(12):937–43.
60. Berlowitz DR, Ash AS, Hickey EC, Friedman RH, Glickman M, Kader B, et al. Inadequate management of blood pressure in a hypertensive population. N Engl J Med. 1998;339(27):1957–63.
61. Aziz H, Hatah E, Makmor Bakry M, Islahudin F. How payment scheme affects patients' adherence to medications? A systematic review. Patient Prefer Adherence. 2016;10:837–50.

62. Schoen C, Osborn R, Doty MM, Squires D, Peugh J, Applebaum S. A survey of primary care physicians in eleven countries, 2009: perspectives on care, costs, and experiences. Health Aff. 2009;28(6):w1171–83.
63. Morrison V, Fragher E, Parveen S, Plumpton C, Cylne W, De Geest S, et al. Determinants of patient adherence to antihypertensive medication: a multi-national cross-sectional survey. 2012: 78–103 pp.
64. Schafheutle EI, Hassell K, Noyce PR, Weiss MC. Access to medicines: cost as an influence on the views and behaviour of patients. Health Soc Care Community. 2002;10(3):187–95.
65. Croog SH, Levine S, Testa MA, Brown B, Bulpitt CJ, Jenkins CD, et al. The effects of antihypertensive therapy on the quality of life. N Engl J Med. 1986;314(26):1657–64.
66. Flack JM, Novikov SV, Ferrario CM. Benefits of adherence to anti-hypertensive drug therapy. Eur Heart J. 1996;17(Suppl A):16–20.
67. Dusing R, Weisser B, Mengden T, Vetter H. Changes in antihypertensive therapy—the role of adverse effects and compliance. Blood Press. 1998;7(5–6):313–5.
68. Caro JJ, Speckman JL, Salas M, Raggio G, Jackson JD. Effect of initial drug choice on persistence with antihypertensive therapy: the importance of actual practice data. CMAJ. 1999;160(1):41–6.
69. Bloom BS. Continuation of initial antihypertensive medication after 1 year of therapy. Clin Ther. 1998;20(4):671–81.
70. Payne KA, Esmonde-White S. Observational studies of antihypertensive medication use and compliance: is drug choice a factor in treatment adherence? Curr Hypertens Rep. 2000;2(6):515–24.
71. Burnier M, Brunner HR. Angiotensin II receptor antagonists. Lancet. 2000;355(9204):637–45.
72. Conlin PR, Gerth WC, Fox J, Roehm JB, Boccuzzi SJ. Four-Year persistence patterns among patients initiating therapy with the angiotensin II receptor antagonist losartan versus other artihypertensive drug classes. Clin Ther. 2001;23(12):1999–2010.
73. Neaton JD, Grimm RH Jr, Prineas RJ, Stamler J, Grandits GA, Elmer PJ, et al. Treatment of Mild Hypertension Study. Final results. Treatment of Mild Hypertension Study Research Group. JAMA. 1993;270(6):713–24.
74. Philipp T, Anlauf M, Distler A, Holzgreve H, Michaelis J, Wellek S. Randomised, double blind, multicentre comparison of hydrochlorothiazide, atenolol, nitrendipine, and enalapril in antihypertensive treatment: results of the HANE study. HANE Trial Research Group. BMJ. 1997;315(7101):154–9.
75. Vrijens B, Sotiris A, Burnier M, de la Sierra A, Volpe M. Current situation of medication adherence in hypertension. Fornt Pharmacol. 2017;8:100.
76. Fargher E, Plumpton C, Morrison V, Hughes D. Preferences for persistence with medications: results froma mulit-national discrete choice experiment. 2012: 104–26 pp.
77. Ingersoll KS, Cohen J. The impact of medication regimen factors on adherence to chronic treatment: a review of literature. J Behav Med. 2008;31(3):213–24.
78. Dunbar-Jacob J, Bohachick P, Mortimer MK, Sereika SM, Foley SM. Medication adherence in persons with cardiovascular disease. J Cardiovasc Nurs. 2003;18(3):209–18.
79. Eisen SA, Miller DK, Woodward RS, Spitznagel E, Przybeck TR. The effect of prescribed daily dose frequency on patient medication compliance. Arch Intern Med. 1990;150(9):1881–4.
80. Lee JY, Kusek JW, Greene PG, Bernhard S, Norris K, Smith D, et al. Assessing medication adherence by pill count and electronic monitoring in the African American Study of Kidney Disease and Hypertension (AASK) Pilot Study. Am J Hypertens. 1996;9(8):719–25.
81. Yiannakopoulou E, Papadopulos JS, Cokkinos DV, Mountokalakis TD. Adherence to antihypertensive treatment: a critical factor for blood pressure control. Eur J Cardiovasc Prev Rehabil. 2005;12(3):243–9.
82. Iskedjian M, Einarson TR, MacKeigan LD, Shear N, Addis A, Mittmann N, et al. Relationship between daily dose frequency and adherence to antihypertensive pharmacotherapy: evidence from a meta-analysis. Clin Ther. 2002;24(2):302–16.

83. Chapman RH, Benner JS, Petrilla AA, Tierce JC, Collins SR, Battleman DS, et al. Predictors of adherence with antihypertensive and lipid-lowering therapy. Arch Intern Med. 2005;165(10):1147–52.
84. George J, Shalansky SJ. Predictors of refill non-adherence in patients with heart failure. Br J Clin Pharmacol. 2007;63(4):488–93.
85. Burnier M, Brown RE, Ong SH, Keskinaslan A, Khan ZM. Issues in blood pressure control and the potential role of single-pill combination therapies. Int J Clin Pract. 2009;63(5):790–8.
86. Pan F, Chernew ME, Fendrick AM. Impact of fixed-dose combination drugs on adherence to prescription medications. J Gen Intern Med. 2008;23(5):611–4.
87. Gerbino PP, Shoheiber O. Adherence patterns among patients treated with fixed-dose combination versus separate antihypertensive agents. Am J Health Syst Pharm. 2007;64(12):1279–83.
88. Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis. Hypertension. 2010;55(2):399–407.
89. Sherrill B, Halpern M, Khan S, Zhang J, Panjabi S. Single-pill vs free-equivalent combination therapies for hypertension: a meta-analysis of health care costs and adherence. J Clin Hypertens. 2011;13(12):898–909.
90. Comte L, Vrijens B, Tousset E, Gerard P, Urquhart J. Estimation of the comparative therapeutic superiority of QD and BID dosing regimens, based on integrated analysis of dosing history data and pharmacokinetics. J Pharmacokinet Pharmacodyn. 2007;34(4):549–58.

Beliefs and Adherence in Hypertension and Cardiovascular Protection

10

Amy Chan and Rob Horne

10.1 Non-adherence: The Silent Thief

10.1.1 Sizing the Challenge of Non-adherence

The availability of medicines for cardiovascular protection has the ability to add on years of life to individuals at risk of cardiovascular events—if everyone aged 55 or older, or had existing cardiovascular disease, took medications for cardiovascular protection, a third of the individuals would gain an average of 11 years of life, free from cardiovascular events or stroke [1]. The greatest challenge, however, lies in achieving adherence to these preventative treatments. Whilst the use of medicines for cardiovascular protection have the potential to reduce risk by over 80% [1], these health benefits cannot be gained if individuals do not take the treatment.

Adherence to treatment in long-term conditions where medication primarily serves as a preventative, rather symptomatic or curative, measure is notoriously difficult [2]. Medication used for hypertension and cardiovascular protection are no exceptions. Patients prescribed such treatments are frequently asymptomatic, and correspondingly the risk of early treatment discontinuation is high [3]. Prescriptions for newly prescribed medicines for hypertension or hyperlipidaemia have the highest rates of primary non-adherence—that is, the prescription is not even brought to the pharmacy to be filled—compared to other medication classes [4]. Rates in the literature suggest that nearly 1 in 3 new prescriptions for hypertension or hyperlipidaemia are never filled [4]. Even when medicines are started by patients, the likelihood of continuation in the long term is low. A study of 77,193 patients on antihypertensive treatment found that after 2 years of treatment, only 55% of

A. Chan · R. Horne (✉)
Centre for Behavioural Medicine, Department of Practice and Policy, UCL School of Pharmacy, University College London, London, UK
e-mail: amy.chan@ucl.ac.uk; r.horne@ucl.ac.uk

M. Burnier (ed.), *Drug Adherence in Hypertension and Cardiovascular Protection*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-76593-8_10

patients remained on treatment [3]. This was further reinforced in a meta-analysis which included 20 studies investigating adherence to medicines used in cardiovascular prevention, such as aspirin, statins, and antihypertensives: after 24 months, adherence was estimated to average 57% [5], a percentage similarly echoed in a meta-analysis published in the following year [6].

These numbers are potentially deadly. For every preventative medication that is never started, missed, or stopped early, there is a corresponding increase in risk of adverse health outcomes. Patients who did not fill their discharge prescriptions within 120 days after a myocardial infarction had an 80% increased odds of death; those who filled part of their prescriptions had a 44% increased odds, compared to those who filled the majority of their prescriptions [7]. It is well documented in the literature that poor medication adherence is linked to poor health outcomes; likewise, good adherence is linked to good health outcomes [8]. Early discontinuation of antihypertensive treatment, for example, was associated with a 15% increased risk of acute myocardial infarction and a 28% increased risk of stroke [3]. Similarly, in a large population-based retrospective study of 31,306 patients, patients who had good or excellent adherence to antihypertensive treatment had almost half the risk of all-cause death, stroke, or acute myocardial infarction (hazard ratio 0.69 with good adherence and 0.53 with excellent adherence) compared to those with poor adherence [9]—a finding which has been replicated in a number of other studies for antihypertensives as well as other cardiovascular protection agents [6, 10, 11]. The consequences of non-adherence are therefore great—not only for the individual in terms of lost years of life and disability but also for health providers, payers, and society. Patients who have poor adherence to their antihypertensive therapy are at higher risk of developing cardiovascular disease such as coronary disease or chronic heart failure [12]. It is the silent thief of resources—cost reductions in the order of 10–18% are estimated between groups with high and low adherence [13]. Yet despite the vast amount of evidence highlighting the importance of adherence to preventative treatment in hypertension and cardiovascular disease, adherence remains suboptimal.

Non-adherence is one of the most important challenges facing healthcare today. Although effective preventative medications exist for cardiovascular protection, which have proven potential to save lives, non-adherence as a cause of ongoing morbidity and mortality has not been adequately addressed. If the prescription was appropriate, non-adherence represents a waste of resources and a significant missed opportunity for health gain. As stated in the World Health Organisation report on adherence, “the potential rewards for patients and societies of addressing adherence to long-term therapies are large” [2]. There is an urgent need to design more effective solutions to address non-adherence.

10.2 Interventions to Enhance Adherence in Cardiovascular Disease: Room for Improvement

10.2.1 Review of over 20 Years of Intervention Research

Over the last two decades, there have been an increasing number of interventions designed to address the issue of non-adherence in long-term conditions. The latest

Cochrane review published in 2014 included 182 published randomised controlled trials (RCTs) of adherence interventions—an increase of 109 RCTs since the previous review in 2007 [14]. This increasing trend in number of studies is likely to continue as the challenge of non-adherence remains. Of the RCTs included in the review, the majority (24%, $n = 44$) of the RCTs were in the hypertension, dyslipidaemia, and cardiovascular disease or risk, highlighting the increasing prevalence of these conditions. Of the included RCTs however, only 2 RCTs in hypertension were considered to have low risk of bias and were included in the analysis [15, 16]. Both of these RCTs involved multifaceted, complex interventions, which are likely to be difficult to replicate in a real-world clinical setting. In a landmark study by Haynes et al., the intervention included special pill containers, counselling, self-monitoring, reminders, feedback, and support groups administered biweekly by a programme coordinator. Despite this intensive intervention and the corresponding higher adherence achieved in the intervention group, no significant changes were seen in diastolic blood pressure after 6 months [15]. In the study by Morgardo et al., intervention patients received counselling from a hospital pharmacist at a specialised outpatient clinic, providing education, advising physicians, and verifying adherence through checking of blister packs and medication boxes. Both adherence and blood pressure control improved after 9 months [16]. Even when all studies are taken into account, the effects of these interventions on adherence are mixed and non-consistent.

As these examples demonstrate, many adherence interventions are complex. There is a lack of high-quality evidence to support the use of one particular intervention over another as results vary from one study to the next—whilst education may be effective in one population, this is ineffective in another. Despite the increasing number of intervention studies, the conclusion from these systematic reviews remains unchanged across 20 years of research. Interventions to improve adherence have limited effectiveness, and even if studies do show effect, the interventions are complex and difficult to sustain in real-life practice. Even the best interventions have limited and short-lived effects. Details on the actual content and delivery of the interventions are commonly not described in sufficient detail to replicate in practice. Systematic reviews may also not be able to capture changes in behaviour in an individual over the duration of the study. Although large numbers of studies are included in systematic reviews, the use of inter-group comparisons in RCTs may not capture intra-individual changes in behaviour. These changes may provide essential clues as to how the patient interacts with the intervention, and what factors determine its effectiveness. Unfortunately, few studies capture these details of individual behaviour change and few describe interventions in sufficient detail for us to identify the factors that were important for the behaviour change, or for replication. There is a need for a different approach to adherence—one that enables us to gain in-depth understanding of the barriers and facilitators of adherence to allow the design of effective interventions in a sustainable manner. Few interventions are tailored to address the specific reason for non-adherence that are unique to the individual [17, 18].

Although many different types of adherence interventions have been trialled in hypertension and cardiovascular protection, the techniques used and outcomes seen vary widely between studies, even amongst studies using the same general

intervention technique. Interventions which have been trialled include education; motivational interviewing; adherence problem solving; targeting adherence barriers; medication packaging; reminders; instructions; social support; self-monitoring; care integration; and adherence feedback [19]. Yet despite the vast number of interventions trialled, no single approach has been identified which effectively addresses non-adherence consistently—in fact, some studies which incorporate adherence changing techniques (such as problem-solving strategies) appear to report smaller effect sizes than studies which do not use these techniques [19].

Although no evidence supports any particular intervention type over another, interventions which appear to be more effective tend to be ones which involve multiple intervention components; or target patients recruited specifically due to adherence problems; or involved intervention delivery over a sustained period [19, 20]. These provide some clues as to what an effective intervention might look like. We can gain further information from studies which explore relationships between particular patient characteristics and adherence; although these studies per se give minimal information on how to develop an effective intervention, the findings can help identify groups at high risk of poor adherence and thus allow targeting of adherence interventions. For example, a systematic review and meta-analysis of adherence interventions in hypertension found that effect sizes were larger for interventions amongst female, older and moderate- or high-income participants [19]. These findings can have implications when prioritising interventions in limited resource settings. However, when considering the design of effective interventions, one must look beyond the population and focus on the individual. Interventions that may have demonstrated effectiveness in one population may not be effective for a particular individual. There is a need for an individualised, tailored approach if effective interventions are to be designed.

10.3 Understanding Non-adherence as a Variable Behaviour

10.3.1 Adherence as a Behaviour, Not a Characteristic

Adherence has traditionally been viewed as a characteristic unique to an individual—a person was thought of as either adherent or non-adherent. Yet the possible reason why previous interventions have failed to demonstrate effectiveness may lie in the approach taken to address non-adherence. Past research has focused predominantly on attempting to explain adherence using quantifiable determinants such as patient, regimen, or illness characteristics [21]. However, as discussed previously, these determinants have limited value when attempting to explain adherence. The ‘non-adherent patient’ is a myth as most of us can be non-adherent at least some of the time [17]. The relationships observed between particular characteristics, such as sex or income, and adherence, are neither clear nor consistent. For example, a study of 2325 patients on antihypertensives found an association between younger age and poorer adherence [22], yet a similar study found that those who were older were less likely to adhere to treatment [23]. The same contradicting associations have been reported with other demographic characteristics such as income and sex.

Indeed, focusing on sociodemographic factors will not provide a solution to non-adherence; non-adherence is a feature of the way the individual interacts with their treatment rather than any particular characteristic of the patient themselves. Non-adherence is therefore best viewed as a variable behaviour rather than a trait characteristic as adherence behaviour varies not only between individuals, but even within the same individual over time. Non-adherence does not arise from irrational behaviour—more often than not, the individual goes through a cognitive process and their consequent behaviour or actions towards the treatment comes from a combination of their own personal experiences with treatment, their perceptions of health and medication in general, and the attitudes they develop about their condition and treatment [17].

The best insights we can gain into adherence behaviour is to understand an individual's perceptions about their illness and treatment. Indeed, patients' understanding of the causes and effects of hypertension and beliefs about side effects were some of the most commonly reported reasons for stopping treatment for hypertension [24]. Patients who believe they are personally able to control the illness without treatment are almost half as likely to adhere to adhere to treatment [24, 25]. These findings are similar with medicines prescribed for cardiovascular disease [26]. Together these studies illustrate the importance of understanding adherence as a behaviour—a person's beliefs about the illness and treatment are more likely to influence adherence rather than demographic characteristics. Future interventions in adherence need to focus on changing behaviour and using behaviour change techniques [27]. New strategies need to build on this concept of adherence as a health behaviour to enable effective interventions to be developed. After decades of research, it is clear there is no one type of patient who is 'non-adherent', nor a 'one size fits all' intervention. There is a need to develop more effective ways of tailoring support to meet the needs of individuals if we are to improve adherence in a sustainable fashion.

10.3.2 The Motivation-Ability Paradigm for Explaining Adherence Behaviour

In order to tackle non-adherence, it is important to understand why non-adherence occurs from an individual patient perspective. First, non-adherence may be intentional (e.g. when we decide not to take the treatment or to take it in a way which differs from the recommendations) and/or unintentional (e.g. when we want to follow the recommendations but lack the capability or opportunity to do so). The easiest way to think of this is to consider adherence behaviour as two-pronged—patients do not adhere because either they **do not want to**, or they **are not able to**. How non-adherence arises therefore relates to two components which drive the behaviour respectively—*motivation* and *ability* [17]. This ability in turn is affected by the individual's *environment*—both internal factors (e.g. physical capability to take the medication) and external factors (e.g. aspects of our environment affecting access to the treatment, such as not having easy access to a pharmacy) [17, 28].

This forms the basis of the Perceptions and Practicalities Approach (PAPA) to explaining and improving adherence [17], which has been applied in the NICE Medicines Adherence Guidelines [18].

10.3.3 A Perceptions and Practicalities Approach to Designing Patient-Centred Interventions

Using PAPA for adherence support derives from an understanding of the types of reasons why people do not take their medicines (Fig. 10.1). First, adherence to treatment is a result of two factors: motivation and ability, as described above. PAPA therefore stipulates that adherence interventions should address these two components: *motivation* to adhere by addressing perceptual barriers (e.g. beliefs about the illness and treatment) and *ability* to adhere by minimising practical barriers (e.g. ability to remember to take the medicine, or afford medication supply) [18]. Adherence support should be tailored to the individual's need by using a 'menu-based' approach. This is where specific intervention components are selected to address the individual's unique perceptual and/or practical barriers.

Figure 10.1 shows the PAPA approach to adherence—it depicts the key influences of adherence behaviour as the two middles circles, which represent perceptual and practical barriers to adherence. These two factors can overlap. For example, motivation may help the individual overcome limitations in ability which might in turn influence motivation to take the treatment. The model is therefore a Venn diagram, rather than two discrete circles (Fig. 10.1). Influencing these two factors is the social and environmental context affecting the interaction of the patient with their medication [17]. The importance of these external factors (e.g. social and environmental factors, or triggers to act such as reminders) is also described in other behaviour change models, such as in the Fogg Behaviour Model which identifies external triggers as an impetus for action [29], and Michie et al.'s COM-B conceptual framework for determinants of behaviour [30], which describes capability, opportunity and motivation as components which act together to affect behaviour.

Adherence is therefore best understood as a complex behaviour with multiple determinants—both internal and external (see Fig. 10.2 for a summary). These

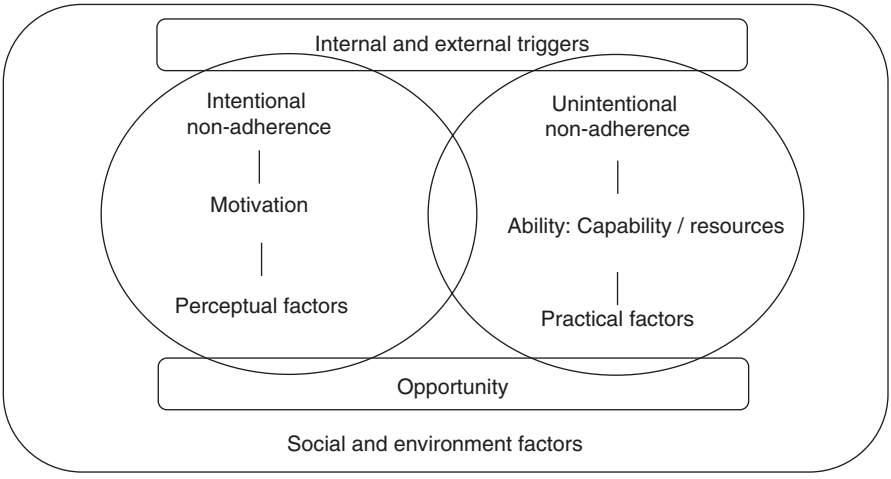


Fig. 10.1 Figure depicting PAPA: how motivation and ability overlap with other factors to influence adherence

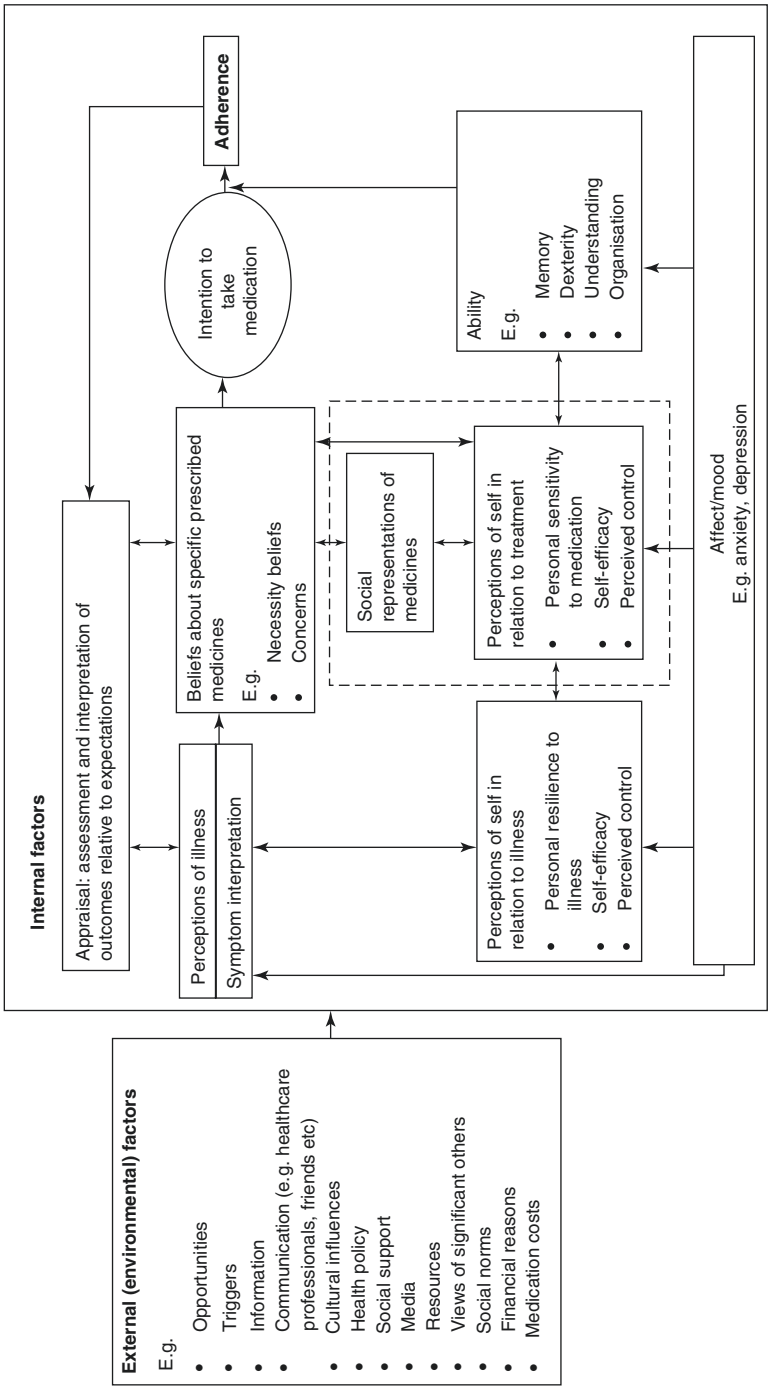


Fig. 10.2 Conceptual map of determinants of adherence (reproduced from Horne et al., 2005 [17])

factors form part of a complex interplay of determinants influencing behaviour. The 'internal' factors influencing motivation and ability may be moderated by 'external' variables, such as the quality of the patient-provider relationship [31], and also be wider societal contexts such as funding and financial coverage of treatment [24]. The external factors can include whether the individual has the opportunity to adhere to treatment; as well as external triggers to act such as text message reminders to prompt behaviour [32].

When considering how to design adherence interventions, these adherence determinants can be used to help target interventions. Motivation and ability can be considered separately based on what factor or factors are driving the behaviour. For example, interventions to improve a patient's *ability* to adhere (such as improving access to treatment) will fail if the patient does not *want* to take the medication (such as when the patient decides they do not need medication). Understanding what drives a patient's decision to take, or not take, a treatment is key to addressing non-adherence. The following sections explore these two drivers of non-adherence—perceptions and practicalities—in greater detail.

10.3.3.1 Perceptions: Understanding How Beliefs About Necessity and Concerns About Medication Influence Decisions about Treatment

When a person starts a new medication, they will begin to form their own beliefs and attitudes towards the treatment based on their initial and subsequent evaluation of the medication. This thinking process is captured by the Necessity-Concerns Framework [33]. The framework suggests that the motivation to start and persist with treatment is influenced by the way the individual judges their personal *need* for the treatment relative to their *concerns* about potential adverse effects. Analysis of 514 patients on antihypertensives found those who believed in the necessity of the treatment had triple the odds of adhering than those who did not [25]. Similarly, adherence is also affected by concerns about adverse effects—a phenomenon which may account for the differences in adherence rates with different antihypertensive classes [34, 35]. Diuretics, for example, are commonly associated with poorer adherence rates compared to newer agents such as angiotensin II receptor antagonists, which may have a better perceived side effect profiles [35]. Other studies that investigated patients with a range of other conditions have consistently found similar results—that poor adherence is related to doubts about personal need for medication and concerns about potential side effects [36].

Treatment Necessity Beliefs

Beliefs about the importance and necessity of medicines can have a significant impact on adherence. Qualitative studies show that many people hold prototypic beliefs about medicines, and their capacity to produce harm as well as benefit, and beliefs about the appropriateness of doctors' prescribing of medication [33]. These beliefs exist even before a person takes the medication. When a person is first presented with a new diagnosis, or health 'threat', the first thing they will try to do is to

make sense of the situation, based on the thoughts they had about condition even before they were diagnosed. These thoughts will then influence how information is interpreted by patients, what their experiences are, and how they act as a result of this information [17, 37]. A qualitative synthesis of studies into the lay perspectives of hypertension found that many people believe hypertension is caused by stress, and as such regular treatment is not needed if the stress abates or they are able to reduce their stress [24, 38].

Likewise, it is intuitive that medicines should only be taken when we are feeling ill. After all, for many patients, the 'no symptoms, no medication' concept will be much more familiar than needing to take medication when they do not perceive themselves to be unwell. This is illustrated in the difference in adherence rates seen between medications prescribed for primary versus secondary prevention. Adherence to medicines for cardiovascular protection averages 50% when used in primary prevention; this increases to an average of 66% in secondary prevention [5]. This difference can be explained by how the individual makes sense of the need to take regular medication—it makes 'sense' for an individual to be on treatment after having a cardiac event, but perhaps less so for prevention. Adherence for secondary prevention purposes would thus be expected to be higher as the individual is able to make sense of the need for treatment [5].

Patients who believe in the necessity of treatment have a much higher chance of adhering to treatment compared to those patients who did not perceive treatment as necessary [25]. This appears to be particularly problematic for cardiovascular medication as many perceive a limited necessity for medicines, and believe there is a clear link between the condition and lifestyle choices [26, 39] compared to other health conditions such as diabetes and thus do not see regular treatment as necessary. These beliefs make patients particularly resistant to having additional medications for cardiovascular medication, and fuel the belief that health professionals tend to overprescribe medicines [26].

Perceived necessity of treatment is however not related to beliefs about treatment efficacy. Although views about medication efficacy are likely to contribute to perceived need, the two are not synonymous. For example, perceived necessity can be influenced by illness beliefs—a patient might believe that a treatment is effective but may not perceive a personal *need* for the treatment. For example, a patient may believe antihypertensives are effective for reducing blood pressure, but may not think their blood pressure needs treating with a medication, such as when they believe it is related to stress [24]. In this case, the patient does not think they need any pharmaceutical treatment, regardless of its perceived efficacy. Conversely, a patient might perceive a strong need for a treatment even though they believe it is only moderately effective—for example, if it is the only treatment that is available or acceptable to the patient. A study of beliefs about hypertension in different culture groups found that although all respondents understood the importance of controlling hypertension, those of West Indian decent had lower adherence rates to antihypertensives as they preferred treatment with herbal remedies rather than prescribed medicines [38].

Treatment Concerns

In terms of perceived concerns, there is much overlap in the type of concerns that patients report about medicines, regardless of the medication type. Many patients receiving regular medication who have not experienced adverse effects worry about possible problems in the future—a view that may be related to beliefs that regular medication use can lead to dependence or accumulation within the body and corresponding long-term effects [33]. For example, a common concern people have about antihypertensive medication relates to side effects and fear of addiction [24]. These attitudes are linked to wider concerns about scientific medicine in general, a lack of trust in doctors and an increasing interest in alternative or complementary healthcare [33, 38]. People also seem to vary in their perceptions of personal sensitivity to medicines [40], with some being more concerned than others about their response to medication.

The way that people perceive medication in general can influence how people evaluate *specific* medication prescribed for a particular condition [33]. These beliefs can affect a person's initial expectations of the outcome of taking a medication as well as how any subsequent events are interpreted—for example, whether symptoms experienced are attributed to the illness or the medication [41]. These beliefs may even influence clinical outcome directly via the 'placebo/nocebo' effects of active drugs—terms describing the phenomenon of having beneficial or harmful effects occur when people have positive or negative expectations about the medication, respectively [42]. Beliefs can also be *specific* for a particular medication—such as when adherence to certain antihypertensive medications are higher for particular classes [35].

Concerns also relate to the meaning that being on regular medication has for the individual and their sense of self or identity. Taking a daily treatment may be an unwelcome reminder of their illness which may have a negative impact on how they view themselves or perceive how they are seen by others. A study into beliefs about hypertension in 19 African American males showed that having hypertension was viewed by some as being "weak" or "not macho" and that it is seen as a "basically a Black disease"—ideas which can add to negativity and stigma [43]. In these circumstances, non-adherence might be seen as an implicit strategy to minimise the impact on their sense of self [43]. These necessity beliefs and concerns can influence adherence separately and in combination, and the effects may be through explicit and implicit processes. For example, in some situations, non-adherence could be part of a deliberate strategy to minimise harm by taking less medication. Alternatively, it might simply reflect the fact that patients who do not perceive their medication to be important are more likely to forget to take it. The impact of perceptions of treatment on adherence may also influenced by beliefs about adherence behaviour itself, such as whether or not strict adherence to medication is needed to achieve the desired outcome. This is seen when patients decide to take 'drug holidays', where they believe they can go without medication for a certain period of time [43].

Common Sense Understanding of Illness and Treatment

Adherence in hypertension and cardiovascular is traditionally difficult to achieve. Whilst non-adherence is a problem that is common to all health conditions where regular preventative treatment needs to be taken, medicines prescribed for hypertension or cardiovascular protection pose unique challenges. Qualitative research into patient perceived barriers to adherence provides us with some clues as to why adherence in this group of conditions may be particularly difficult. Firstly, hypertension and cardiovascular disease are predominantly silent conditions—people tend to feel well most of the time and may have limited experience of co-morbidities or medication when they are first informed of hypertension or cardiovascular risk [44, 45]. Surveys of patients on antihypertensive agents have found that fear of adverse effects is a significant barrier to adherence, particularly amongst those who are young or in the early stages of treatment [24, 45]. Indeed, patients who were on multiple drug treatments, or have other co-morbidities such as diabetes or dyslipidaemia, were more likely to adhere to their antihypertensive treatments compared to their counterparts who did not have other treatments or cardiovascular co-morbidities [10]. Likewise, patients who have pre-existing hypertension, or a history of cardiac disease and are prescribed medication for secondary prevention, have higher adherence rates compared to patients who are newly prescribed treatment, or do not have a history of a cardiac event [5, 46].

Secondly, it is difficult for the patient to perceive any immediate benefits or differences from taking the medication. Although there is plenty of evidence highlighting the clinical benefits of medication taking for cardiovascular protection, it is difficult for the patient to detect these benefits on an individual subjective scale. Furthermore, there are no immediate physical consequences or symptoms that arise from missing doses—even if doses are missed for a prolonged period—thus further reinforcing the notion that the medication does very little for improving health [24]. Conversely, even though there are no perceivable benefits of treatment, the patient may suffer from adverse effects when they start the medication—an occurrence which is likely to further deter patients from taking their medication. There is a link between reported side effects and lowered treatment adherence—in a study of 175 patients on antihypertensive treatment, those individuals who reported a high number of side effects beyond the median value in the group had lower adherence; those who reported genitourinary side effects such as excessive urination or reduced sexual drive were least likely to adhere to treatment [47]. These quantitative findings are supported by qualitative research identifying side effects—in particular urinary frequency and impotence—as reasons for non-adherence [24].

Lastly, hypertension and cardiovascular disease tend to be perceived by people as self-manageable conditions, conditions which can be easily managed by the individual themselves, such as by reducing stress for example [24]. The role of medication is thus perceived to be of limited value, as many individuals link lifestyle factors with hypertension and cardiovascular disease, and thus believe that if their lifestyle improved, their need for these medicines would be reduced [26].

It can therefore be very difficult to convince a patient of their need for treatment and the potential benefits they can gain from taking treatment regularly. Indeed, there can be little impetus for patients to begin taking a new treatment for a condition from which they do not suffer any ill effects. Even if patients do begin to take the treatment, the likelihood of continuing this medication everyday lifelong is very low—a fact which is reflected in the high rates of discontinuation—persistence with medication drops within the first 6 months of starting antihypertensive or cardiovascular protection treatment, and continues to decline over time, with less than half of the individuals persisting after 2 years [3, 7, 44]. Studies report reductions in adherence to antihypertensives by 20-30% over a period of 1–3 years after starting medication [46, 48], with similar trends seen for other cardiovascular protection agents such as statins and aspirin [5, 7]. Given the increasingly prevalence of cardiovascular diseases, and the great potential of these preventative medicines to improve outcomes and extend life, there is a need to focus on improving adherence to these treatments and maximise the efficacy of treatments.

10.3.3.2 Practicalities: Enhancing Capability, Opportunity and Triggers to Adhere

The other key factor influencing adherence are practical barriers—factors that determine a patient's ability to adhere. Forgetting to take the medication is the most commonly cited practical barrier for non-adherence [39]. This may be due to the complexity of regimes associated with cardiovascular diseases as well as a lack of routine and erratic lifestyle. Regimens with a high dosing frequency, or high number of medication or complicated instructions for medication taking tend to be associated with poorer adherence [34, 35]. Reducing dosing frequency to once daily can improve the patient's ability to adhere by making the treatment less intrusive and more convenient [34, 49]. Simplifying the regimen by using fixed dose combination agents or reducing unnecessary polypharmacy can also facilitate adherence [10].

Reminder systems or medication organisers such as pill boxes may be useful though reported effects are typically modest [50]. Linking the medication taking to specific environmental cues may be more effective than a repeated reminder to help reinforce habits and routine [51]. For example, placing the medication near the toothbrush so that taking the medication becomes linked to an existing habit may be useful. This involves planning with the patient how and when they can take their medication. Turning a patient's intention to take medication (e.g. 'I will take my medicine') into a more specific plan (e.g. 'I will take my medicine immediately after I brush my teeth every morning') increases the likelihood of the behaviour being performed [51], though routines can be susceptible to changes in the environment such as going on holiday [52].

Strategies to improve adherence by changing formulation or dosing are however only effective if perceptual barriers to adherence have been addressed [17]. Involving patients in treatment decisions is therefore important to achieve ongoing

adherence [53]. To achieve adherence, the clinician must therefore aim to elicit the patient's perspective about treatment—including their beliefs and concerns—and ensure that decisions about treatment are informed by fact rather than misperceptions [54]. Offering a medication choice can be an effective method of involving the patient in prescribing decisions—even as simple as involving the patient in choice of dosage form may be a helpful way of helping the patient feel cared for and involved [43]. Medication cost and access to health services and medication may be other factors to consider when addressing practical barriers to adherence [39, 49].

10.4 Assessing Non-adherence

Measuring non-adherence is a complex issue. Whilst the easiest and most accessible method of assessing adherence is simply to ask the patient, it comes with the caveat that the reported adherence is likely to be much higher than what the true adherence might be [55]. For example, a meta-analysis found that average adherence to medicines used for cardiovascular protection was estimated to be 90% in studies which used self-reported measures of adherence, whereas studies using prescription refills to measure adherence reported average adherence to be 57% [5]. This phenomenon has been described extensively in the literature (Self report bias) and can be explained by 'social desirability bias'—where the patient wishes to 'please' the health provider by exhibiting themselves in a more positive light when reporting their treatment adherence.

The use of more accurate objective measures however, such as using high performance liquid chromatography-tandem mass spectrometry-based analysis of urine/serum or electronic adherence monitoring, have their own shortcomings. Urine analysis may be viewed as intrusive or inconvenient by the patient and electronic adherence monitoring—where each dose taken is monitored electronically using a special monitored vial—is expensive and may be ill-perceived by patients as 'big-brother' monitoring [55].

There is therefore the need to encourage patients to actively and accurately discuss adherence with the clinician. The negativity surrounding medication non-adherence needs to be removed to encourage honest, non-judgemental communication between the patient and healthcare provider [18]. In clinical practice, 'detoxifying' non-adherence and allowing sufficient time in the consultation to discuss barriers to treatment are necessary first steps to improve the assessment of adherence [18, 53]. This may be facilitated by opening up discussions about adherence in a non-judgemental way and explaining the reasons for the discussion. It is helpful to focus the discussions on a specific time period such as "in the past week" and asking about specific medication-taking behaviours such as skipping or changing the dose, or stopping medication [18]. Patients should be encouraged to freely discuss their adherence behaviours and barriers in clinical practice such that the need for objective adherence measurement becomes less of an issue.

10.5 Using PAPA in Practice to Achieve Informed Adherence

10.5.1 A Stepped Approach to Improving Adherence and Tailoring Support to Individual Need

PAPA provides a pragmatic framework to adherence support. This approach can be used in any consultation about treatment. The first step to this is to aim for 'easy wins' by targeting the adherence barriers that can be addressed using minimal resources (Fig. 10.3). This can then be stepped up to address perceptual barriers, specifically targeting motivation, before finally delivering 'tailored PAPA' according to the individual's unique needs.

When delivering an intervention using the PAPA approach, consider these three components:

1. **Communicate necessity of treatment**. In hypertension and cardiovascular disease, many patients do not believe treatment is necessary as they do not feel ill or they think their condition can be managed by lifestyle changes rather than medication. Discuss with the patient what their understanding is of the condition and reason for medication. Explain the condition and how the medication will influence this, considering the aims of the treatment and what the patient themselves hope to achieve. Focus on how the patient may benefit from the treatment, considering the individual motivations the patient may have, which may not be directly related to the condition.
2. **Elicit and address any concerns raised about treatment**. Use open-ended questions to encourage patients to discuss and ask about their condition and treatment.

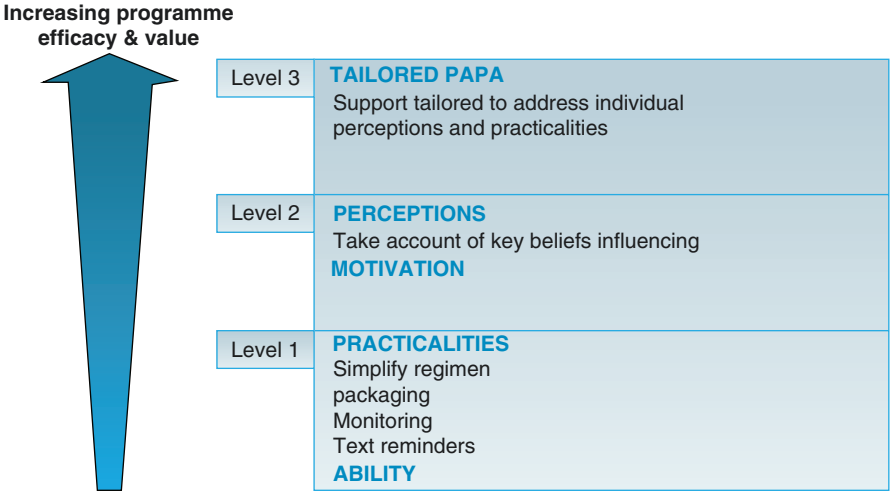


Fig. 10.3 A stepped approach of intervention development according to resource availability. (1) Home R. Project ongoing. (2) Alhalaiqa F, et al. *J Hum Hypertens*, 2012;26:117–26. (3) Farmer AJ, et al. *Diabet Med*. 2016;33:565–79 (Adapted from Horne R, Guide to adherence, Behavioural Pharmacy Programme 2016, UCL School of Pharmacy)

Find out what the patient knows, believes, and understands about their treatment before starting or changing a medicine. Often these concerns centre on side effects of frequent urination or sexual dysfunction, as well as fears of addiction [24]. Discuss and agree a plan of action to manage these concerns with the patient.

3. **Minimise any practical barriers to adherence**. It is helpful to discuss how the patient will fit the medication into their daily routine and remember to take the medication. Identify any barriers and agree a plan of action with the patient.

This approach ensures that both the perceptual barriers (necessity/concern beliefs) and practical barriers are addressed. Previous interventions have had limited effects partly because they have either not addressed all these factors or the intervention has not been individualised to the patient. Many have focussed on single causal factors whereas adherence is best seen as a complex health behaviour with multiple determinants both internal and external (see Fig. 10.2 for a summary). By using this approach, interventions can be tailored to the individual whilst achieving informed adherence.

10.5.2 Providing an Environment for Informed Adherence

Shared decision-marking with the patient and informed choice should be a key facet of clinical practice and adherence. For interventions to be effective, equitable, and efficient, one must facilitate informed choice [17]. Adherence is dependent on a collaborative relationship between the patient and healthcare provider [18]. Key to this is the need to facilitate an honest and open discussion. The discussion should aim to normalise non-adherence and allow patients to report non-adherence and express doubts and concerns. This allows assessment of adherence in a non-judgemental way. Effective communication is important. Factors such as mental state, health literacy, language barriers, or visual or hearing impairment may need to be considered to ensure effective communication.

A patient can be considered to have made an informed choice if they can demonstrate knowledge of relevant information about the treatment and then act according to their beliefs. This concept of informed choice has been extended to informed adherence [56], where evidence-based medicine is used to guide initial treatment recommendations. The recommendations should be presented to patients in a way that takes account of their individual beliefs and preferences, and any incompatibilities between their personal beliefs and the prevailing evidence should be resolved by non-judgemental discussion [37].

10.5.3 Practical Considerations in Intervention Design

When designing and implementing adherence interventions in practice, three dimensions of the intervention need to be optimised for success. This can be remembered as the “3 components to behaviour change” or “3CBC”—content, channel (delivery vehicle) and context.

10.5.3.1 Content

This is the basic substance of the intervention and how the specific barriers and enablers of adherence are addressed. Approaches should be tailored to address both the perceptual factors influencing motivation to initiate and persist with treatment, as well as facilitating the ability to adhere, for example, by addressing any capacity and resource limitations. The PAPA model described above is one method that can be used to ensure all aspects of adherence are addressed. As shown in Fig. 10.3 above, the content of the intervention may start with the simplest intervention (e.g. medication reminders) before progressing to more complex interventions (e.g. tailored advice for perceptual barriers) depending on the time and resources available.

10.5.3.2 Channel

Adherence support should occur, not just at the start of treatment, but also during treatment review as perceptions, abilities, and adherence can change. The increasing use of e-technology and mobile health (such as smart phone apps) offer the prospect of additional channels to compliment practitioner-delivered support [57]. A recent systematic review of the use of mobile technologies in chronic disease identified a total of 13 studies which evaluated mobile adherence tools for cardiovascular disease. Significant improvements in clinical outcomes were reported in 54% of the studies. These studies included use of short message service (SMS) enabled interactive monitoring so that the provider could set reminders for patients, collect data, and schedule visits for treatment adjustments. Others involved salt sensors and remote blood pressure monitoring [57]. However, despite the plethora of technology and digital solutions available, there is as yet, little evidence for their efficacy. Applying the principles outlined above to develop theory-based content might improve their effectiveness and utility.

10.5.3.3 Context

Context considers how appropriate prescribing and adherence support is facilitated by wider contextual factors, such as media representations of treatment and ease of access to treatment. With cardiovascular disease, there are often more than one prescriber involved in the follow-up and prescribing of treatment (e.g. cardiologists and general physicians) which adds to complexities for the patient for managing their treatment. Choudry et al. showed that the more pharmacies and prescribers that were involved in managing treatment, the poorer adherence was to cardiovascular medication [49]. Use of streamlined care and integration of services can help support adherence and facilitate the accessibility of medicines to patients.

Conclusions

Medication non-adherence remains a significant problem today despite decades of adherence intervention research. This non-adherence represents a missed opportunity for health gain, leading to increased risks of morbidity, mortality, and healthcare costs. There is a need for more effective interventions. Recent research recognises the importance of approaching adherence from the

individual's perspective and tailoring the intervention to the unique adherence barriers faced by the individual. For non-adherence to be addressed, future adherence interventions should be designed such that an individual's motivation and ability are taken into account. The use of a perception and practicalities approach to intervention design is one way that can help ensure that the perceptual and practical barriers of the individual are addressed in a tailored and pragmatic manner. By encouraging honest non-judgemental discussions and bringing adherence to the forefront of healthcare, we will be one step closer to tackling this issue of non-adherence. Only then can we fully realise the true benefits of the repertoire of available treatments.

References

1. Wald NJ, Law MR. A strategy to reduce cardiovascular disease by more than 80%. BMJ. 2003;326(7404):1419.
2. Sabaté E. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization; 2003.
3. Breekveldt-Postma NS, Penning-van Beest FJ, Siiskonen SJ, Falvey H, Vincze G, Klungel OH, et al. The effect of discontinuation of antihypertensives on the risk of acute myocardial infarction and stroke. Curr Med Res Opin. 2008;24(1):121–7.
4. Fischer MA, Stedman MR, Lii J, Vogeli C, Shrank WH, Brookhart MA, et al. Primary medication non-adherence: analysis of 195,930 electronic prescriptions. J Gen Intern Med. 2010;25(4):284–90.
5. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. Am J Med. 2012;125(9):882–7.e1.
6. Chowdhury R, Khan H, Heydon E, Shroufi A, Fahimi S, Moore C, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. Eur Heart J. 2013;34(38):2940–8.
7. Jackevicius CA, Li P, Tu JV. Prevalence, predictors, and outcomes of primary nonadherence after acute myocardial infarction. Circulation. 2008;117(8):1028–36.
8. Simpson SH, Eurich DT, Majumdar SR, Padwal RS, Tsuyuki RT, Varney J, et al. A meta-analysis of the association between adherence to drug therapy and mortality. BMJ. 2006;333(7557):15.
9. Esposti LD, Saragoni S, Benemei S, Batacchi P, Geppetti P, Di Bari M, et al. Adherence to antihypertensive medications and health outcomes among newly treated hypertensive patients. Clinicoecon Outcomes Res. 2011;3:47–54.
10. Mazzaglia G, Ambrosioni E, Alacqua M, Filippi A, Sessa E, Immordino V, et al. Adherence to antihypertensive medications and cardiovascular morbidity among newly diagnosed hypertensive patients. Circulation. 2009;120(16):1598–605.
11. De Vera MA, Bhole V, Burns LC, Lacaille D. Impact of statin adherence on cardiovascular disease and mortality outcomes: a systematic review. Br J Clin Pharmacol. 2014;78(4):684–98.
12. Dragomir A, Cote R, Roy L, Blais L, Lalonde L, Berard A, et al. Impact of adherence to antihypertensive agents on clinical outcomes and hospitalization costs. Med Care. 2010;48(5):418–25.
13. Bitton A, Choudhry NK, Matlin OS, Swanton K, Shrank WH. The impact of medication adherence on coronary artery disease costs and outcomes: a systematic review. Am J Med. 2013;126(4):357.e7–e27.
14. Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, et al. Interventions for enhancing medication adherence. Cochrane Database Syst Rev. 2014;(11):CD000011.
15. Haynes RB, Sackett DL, Gibson ES, Taylor DW, Hackett BC, Roberts RS, et al. Improvement of medication compliance in uncontrolled hypertension. Lancet. 1976;1(7972):1265–8.

16. Morgado M, Rolo S, Castelo-Branco M. Pharmacist intervention program to enhance hypertension control: a randomised controlled trial. Int J Clin Pharm. 2011;33(1):132–40.
17. Horne R, Weinman J, Barber N, Elliott R, Morgan M, Cribb A. Concordance, adherence and compliance in medicine taking: report for the National Co-ordinating Centre for NHS Service Delivery and Organisation R & D (NCCSDO). London: NCCSDO; 2005.
18. Nunes V, Neilson J, O'Flynn N, Calvert N, Kuntze S, Smithson H, et al. Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence. London: National Institute for Health and Clinical Excellence; 2009.
19. Conn VS, Ruppar TM, Chase JA, Enriquez M, Cooper PS. Interventions to improve medication adherence in hypertensive patients: systematic review and meta-analysis. Curr Hypertens Rep. 2015;17(12):94.
20. Cutrona SL, Choudhry NK, Fischer MA, Servi AD, Stedman M, Liberman JN, et al. Targeting cardiovascular medication adherence interventions. J Am Pharm Assoc. 2012;52(3):381–97.
21. Becker MH, Maiman LA. Sociobehavioral determinants of compliance with health and medical care recommendations. Med Care. 1975;13(1):10–24.
22. Van Wijk BL, Klungel OH, Heerdink ER, de Boer A. Rate and determinants of 10-year persistence with antihypertensive drugs. J Hypertens. 2005;23(11):2101–7.
23. Shah NR, Hirsch AG, Zacker C, Wood GC, Schoenthaler A, Ogedegbe G, et al. Predictors of first-fill adherence for patients with hypertension. Am J Hypertens. 2009;22(4):392–6.
24. Marshall IJ, Wolfe CDA, McKevitt C. Lay perspectives on hypertension and drug adherence: systematic review of qualitative research. BMJ. 2012;345:e3953.
25. Ross S, Walker A, MacLeod MJ. Patient compliance in hypertension: role of illness perceptions and treatment beliefs. J Hum Hypertens. 2004;18(9):607–13.
26. Stack RJ, Elliott RA, Noyce PR, Bundy C. A qualitative exploration of multiple medicines beliefs in co-morbid diabetes and cardiovascular disease. Diabet Med. 2008;25(10):1204–10.
27. Michie S, Johnston M, Francis J, Hardeman W, Eccles M. From theory to intervention: mapping theoretically derived behavioural determinants to behaviour change techniques. Appl Psychol. 2008;57(4):660–80.
28. Piette JD, Heisler M, Horne R, Alexander GC. A conceptually based approach to understanding chronically ill patients' responses to medication cost pressures. Soc Sci Med. 2006;62(4):846–57.
29. Fogg BJ, editor. A behavior model for persuasive design. In: Proceedings of the 4th international conference on persuasive technology, ACM; 2009.
30. Michie S, van Stralen MM, West R. The behaviour change wheel: a new method for characterising and designing behaviour change interventions. Implement Sci. 2011;6(1):42.
31. Traylor AH, Schmittdiel JA, Uratsu CS, Mangione CM, Subramanian U. Adherence to cardiovascular disease medications: does patient-provider race/ethnicity and language concordance matter? J Gen Intern Med. 2010;25(11):1172–7.
32. Vervloet M, Linn AJ, Van Weert J, De Bakker DH, Bouvy ML, Van Dijk L. The effectiveness of interventions using electronic reminders to improve adherence to chronic medication: a systematic review of the literature. J Am Med Inform Assoc. 2012;19(5):696–704.
33. Horne R, Weinman J, Hankins M. The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication. Psychol Health. 1999;14(1):1–24.
34. Bloom BS. Daily regimen and compliance with treatment: fewer daily doses and drugs with fewer side effects improve compliance. BMJ. 2001;323(7314):647.
35. Gupta P, Patel P, Štrauch B, Lai FY, Akbarov A, Marešová V, et al. Risk factors for nonadherence to antihypertensive treatment—novelty and significance. Hypertension. 2017;69(6):1113–20.
36. Horne R, Chapman S, Parham R, Freemantle N, Forbes A, Cooper V. Understanding patients' adherence-related beliefs about medicines prescribed for long-term conditions: a meta-analytic review of the Necessity-Concerns Framework. PLoS One. 2013;8(12):e80633.
37. Horne R, Clatworthy J. Adherence to advice and treatment. Health psychology. 2nd ed. Chichester: British Psychological Society and Blackwell Publishing Ltd; 2010. p. 175–88.
38. Morgan M, Watkins CJ. Managing hypertension: beliefs and responses to medication among cultural groups. Sociol Health Illn. 1988;10(4):561–78.

39. Andrade JP, Vilas-Boas F, Chagas H, Andrade M. Epidemiological aspects of adherence to the treatment of hypertension. Arq Bras Cardiol. 2002;79(4):380.
40. Horne R, Faasse K, Cooper V, Diefenbach MA, Leventhal H, Leventhal E, et al. The perceived sensitivity to medicines (PSM) scale: an evaluation of validity and reliability. Br J Health Psychol. 2013;18(1):18–30.
41. Heller MK, Chapman SC, Horne R. Beliefs about medication predict the misattribution of a common symptom as a medication side effect—evidence from an analogue online study. J Psychosom Res. 2015;79(6):519–29.
42. Rief W, Bingel U, Schedlowski M, Enck P. Mechanisms involved in placebo and nocebo responses and implications for drug trials. Clin Pharmacol Therap. 2011;90(5):722–6.
43. Rose LE, Kim MT, Dennison CR, Hill MN. The contexts of adherence for African Americans with high blood pressure. J Adv Nurs. 2000;32(3):587–94.
44. Burnier M. Medication adherence and persistence as the cornerstone of effective antihypertensive therapy*. Am J Hypertens. 2006;19(11):1190–6.
45. Richardson MA, Simons-Morton B, Annegers JF. Effect of perceived barriers on compliance with antihypertensive medication. Health Educ Q. 1993;20(4):489–503.
46. Caro JJ, Salas M, Speckman JL, Raggio G, Jackson JD. Persistence with treatment for hypertension in actual practice. CMAJ. 1999;160(1):31–7.
47. Tedla YG, Bautista LE. Drug side effect symptoms and adherence to antihypertensive medication. Am J Hypertens. 2016;29(6):772–9.
48. Bovet P, Burnier M, Madeleine G, Waeber B, Paccaud F. Monitoring one-year compliance to antihypertension medication in the Seychelles. Bull World Health Organ. 2002;80(1):33–9.
49. Choudhry NK, Fischer MA, Avorn J, et al. The implications of therapeutic complexity on adherence to cardiovascular medications. Arch Intern Med. 2011;171(9):814–22.
50. Boeni F, Spinatsch E, Suter K, Hersberger KE, Arnet I. Effect of drug reminder packaging on medication adherence: a systematic review revealing research gaps. Syst Rev. 2014;3(1):29.
51. Gollwitzer PM, Brandstätter V. Implementation intentions and effective goal pursuit. J Pers Soc Psychol. 1997;73(1):186.
52. Lally P, Gardner B. Promoting habit formation. Health Psychol Rev. 2013;7(sup1):S137–S58.
53. Cohen SM. Concept analysis of adherence in the context of cardiovascular risk reduction. Nurs Forum. 2009;44(1):25–36.
54. Horne R, Parham R, Driscoll R, Robinson A. Patients' attitudes to medicines and adherence to maintenance treatment in inflammatory bowel disease. Inflamm Bowel Dis. 2009;15(6):837–44.
55. El Alili M, Vrijens B, Demonceau J, Evers SM, Hiligsmann M. A scoping review of studies comparing the medication event monitoring system (MEMS) with alternative methods for measuring medication adherence. Br J Clin Pharmacol. 2016;82(1):268–79.
56. Horne R, Weinman J. The theoretical basis of concordance and issues for research. In: Bond C, editor. Concordance: a partnership in medicine-taking. London: Pharmaceutical Press; 2004.
57. Hamine S, Gerth-Guyette E, Faulx D, Green BB, Ginsburg AS. Impact of mHealth chronic disease management on treatment adherence and patient outcomes: a systematic review. J Med Internet Res. 2015;17(2):e52.

Part III

Adherence in Hypertension and CV Protection

Impact of Drug Adherence in Clinical Trials

11

Michel Burnier

11.1 Introduction

Evidence based medicine (EBM) represents the integration of clinical expertise, patient's values, and best available scientific evidence in process of decision making related to patients health care [1]. According to modern standards, the practice of medicine should be based essentially on this concept of EBM. Today, clinical evidence are ranked according to the strength of their freedom from the various biases that characterized medical research. Thus, the highest levels of evidence are those obtained by meta-analyses of several randomized controlled trials (RCT) or evidence obtained from only one RCT. Randomized control trials are supposed to provide the best scientific evidence because they are following a strict protocol, which removes biologic and measurement variability, as well as observer and selection bias. Thus, patients are blindly randomized and both patients and physicians are unaware of the treatment allocation; there is an adequate control group and primary and secondary clinical endpoints, as well as the statistical plan, are well-defined before the study. Moreover, these trials are generally conducted by motivated physicians and highly selected patients ensuring that all procedures are strictly followed. At last, the quality of the follow-up and the number of visits is higher than in normal clinical practice. Therefore, participation in a clinical trial significantly increases adherence to both trial-related and non-trial-related treatments because participants are more involved with their conditions and treatments [2]. This is probably the reason why even patients receiving a placebo tend to improve during their participation in a trial [3] and have a reduced mortality [4].

M. Burnier
Service of Nephrology and Hypertension, Department of Medicine, Centre Hospitalier Universitaire Vaudois (CHUV), University Hospital, Lausanne, Switzerland
e-mail: michel.burnier@chuv.ch

M. Burnier (ed.), *Drug Adherence in Hypertension and Cardiovascular Protection*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-76593-8_11

In randomized clinical trials assessing the efficacy or benefits of a new drug treatment or treatment strategy, it is generally assumed that patients follow strictly the recommendations on how and when to take their medications. Hence, investigators and statisticians consider that drug adherence is almost perfect and since subjects are randomized, any percentage of poor medication adherence should have only a minor impact on RCTs' results because it should be the same in the two groups. Others argued that the pattern of compliance in 'intention to treat' analyses reflects compliance in everyday practice. Therefore, adherence as a factor affecting outcome can be disregarded.

But is it really the case? Is drug adherence really so much better in clinical trials? The purpose of this chapter is to review the data available and to discuss important questions raised by non-adherence in clinical trials. One important aspect is how poor medication adherence can actually affect the level of evidence gathered in RCT in terms of efficacy and safety.

11.2 Medication Adherence in Early and Late Phases of Drug Development

The importance of a good adherence in long-term therapies is widely recognized by all healthcare providers. But, as mentioned by A. Breckenridge and colleagues in a recent review [5], *"variable adherence can also have serious consequences in clinical trials conducted in an ambulatory setting, resulting in confusion in their interpretation and sabotage of accurate estimates of benefit and harms."*

During clinical drug development, several deviations from the prescribed dosing regimens can occur and remain unrecognized if not measured adequately such as a delayed onset, underdosing, intermittent complete lapses, and non-persistence. The level of adherence to study medications varies according to development phase as illustrated in Fig. 11.1 [6]. In phase 1 studies, drug delivery is under strict control and medications are generally administered in centers. Hence, there is no real concern about adherence. The situation changes as soon as study drugs are given ambulatory (phases 2 and 3); then, all issues described above may occur leading to suboptimal adherence and hence to a misinterpretation of collected data. The analysis of a cohort of 16,907 patients with different medical conditions enrolled in 95 clinical studies has clearly demonstrated that the number of patients taking the prescribed study medication(s) decreased progressively during the study so that at day 100, about 20% of patients had discontinued treatment and 12% of those still engaged with the dosing regimen were omitting a fraction of the prescribed doses [6, 7].

The recognition of problems associated with adherence in RCT depends enormously on the quality of the method used to monitor drug adherence during the trial. In the past, Pullar et al. had already summarized the various methods used to monitor adherence in clinical trials and described their limitations [8]. These latter remain basically the same as those encountered today in clinical practice and described in other chapters of this book. As mentioned previously, the most frequent method used in RCT is the pill count and refills records. However, it is well known that these

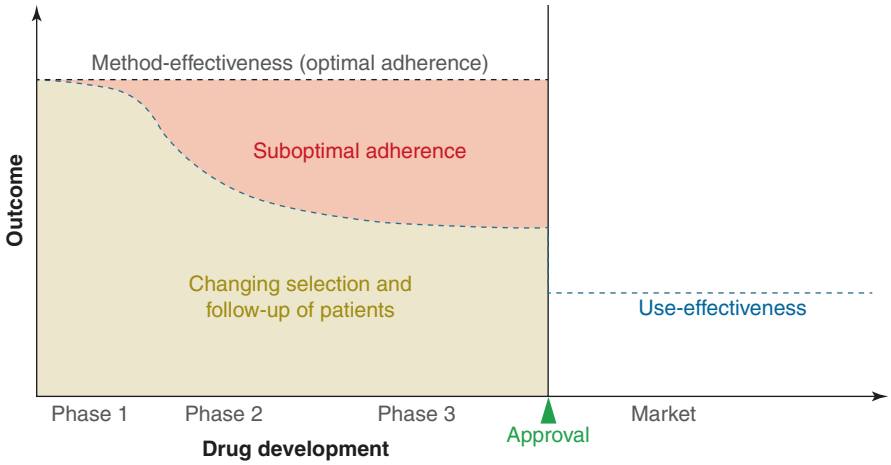


Fig. 11.1 Relationship between outcomes and drug development phases according to the level of adherence to drug therapy (Permission has been obtained from the Journal) (From ref. [6])

two approaches tend to overestimate medication adherence. In addition, these measurements do not provide any information on the dosing history and what patients actually do with their medications. Interestingly, even when measured, authors rarely specify how lack of adherence is dealt with in the handling and interpretation of the data on efficacy and safety.

In recent years, many trials in various therapeutic areas, such as HIV therapy, have been conducted using the MEMS (Medication Events Monitoring System) device alone or in combination with drug measurements. These approaches provide more useful information on how medications were handled by the patients even though the former does not ascertain drug intake. More importantly, data collected with the MEMS enable to perform statistical analyses based on objective measurements of the number of openings or non-openings of the pill box, and to include these analyses in the statistical plan. In the last 20 years, a large experience has been accumulating with the use of the MEMS in clinical trials and the results of more than 700 studies with electronic monitoring of adherence in almost all types of diseases can be found on the following website http://www.medamigo.com/news (verified November 16, 2017). Drug measurements in plasma or urine have now become popular even in clinical trials. However, in order to be interpreted correctly it is important to know the pharmacokinetic characteristics of the measured compound.

Today there is no clear data on the mean percentage of non-adherence in large clinical trials. In a literature review of 192 studies in which pill count was used predominantly to assess adherence, drug adherence was reported to be around 93% [9]. However, from individual datasets one can estimate that poor and/or non-adherence to medication could affect more than 50% of patients enrolled in trials, the percentage increasing with the duration of the trial. [10, 11] As an example, in the EVOLVE trial, a global, multi-center, placebo-controlled, double-blind, event-driven trial (N = 3883) designed to assess the risks and benefits of cinacalcet

compared with placebo along with conventional, standard-of-care therapies, on a composite endpoint consisting of all-cause mortality and major cardiovascular events in patients receiving hemodialysis with moderate to severe secondary hyperparathyroidism, 67% of patients discontinued cinacalcet during the study and 71% stopped the placebo being often switched to commercially available cinacalcet [11]. As we know today, these impressive figures have biased completely the interpretation of the results of EVOLVE. Of note, large discrepancies between pill count and plasma drug levels in clinical studies have been reported suggesting that the actual figures of non-adherence may be much higher than believed [10, 12].

11.3 What Are the Consequences of Non-adherence in Clinical Trials?

As reviewed recently by Breckenridge et al. [5], poor adherence in clinical trials has several major impacts among which a failure to demonstrate efficacy, underestimation of the drug efficacy, and underestimation of safety concerns.

The failure to demonstrate efficacy is perfectly illustrated by the EVOLVE trial and the study of tenofovir as a prophylaxis of HIV infections. Both are excellent examples of apparently negative trials in which statistical analyses were completely biased by a high percentage of non-adherence [10, 11]. Actually, in the case of EVOLVE, performing other statistical analyses than the intention to treat analysis, taking into account the adherence issues could have provided different conclusions and could have demonstrated cardiovascular benefits of cinacalcet [13]. In the end, in both trials, millions of dollars were spent to obtain no clear answers to two important clinical questions.

Underestimation of the real efficacy of drugs and treatment strategies is probably a much more common consequence of a lack of adherence in trials. One example is the re-analysis [14] of the data published by Bobrie et al. [15] who conducted a randomized controlled study in which sequential nephron blockade (SNB) using different diuretics was compared with a sequential blockade of the renin–angiotensin system (RAS) in patients with resistant hypertension. According to the initial analysis, at week 12, the mean between-group difference in daytime ambulatory blood pressure (BP) was 10/4 mmHg in favor of the SNB. The BP goal was achieved in 58% of patients with the combination of diuretics and only 20% with the intensive RAS blockade. In a re-analysis of the data, taking into account drug adherence measured with three different methods, results showed that 64% of patients of the SNB group reached the BP target and the difference between the SNB and the sequential RAS blockade was significant only in those patients who were adherent to the therapy. Of note, in studies comparing drugs, intermittent adherence will of course favor the effect of long-acting drugs and hence will create a bias supporting drugs with long half-lives.

An "*a contrario*" example is the inability of the SIMPLICITY-HTN3 trial [16] to demonstrate the superiority of renal denervation over a sham intervention in patients with resistant hypertension because of a significant decrease in BP in the

control group after sham denervation. This latter can only be explained by a marked improvement of drug adherence during the study due to the involvement of the patients in the trial. Unfortunately, drug adherence was not measured in this trial.

Underestimation of safety concerns is a serious consequence of non-adherence in trials. The impact of non-adherence can underestimate as well as overestimate the side effects of a drug. Indeed, transient interruption of drug therapy or a complete cessation will decrease the time of exposure and hence reduce the likelihood of a side effect. It is important to note that investigators do not always know whether the patient just forgot the medication or voluntarily stopped because of drug intolerance. Reducing the dose or not following the prescription schedule may also blunt the occurrence of side effects. On the other end, stopping and restarting drug therapy might increase the incidence of side effects if the investigational drug induces a withdrawal syndrome or has a strong first dose effect.

As reviewed by Simpson et al. [4], a good adherence is generally associated with a lower mortality in trials (odds ratio 0.56, 95% confidence interval 0.50–0.63). As mentioned earlier, a good adherence to placebo is even associated with a lower mortality (OR 0.56, 95% CI 0.43–0.74), as is good adherence to beneficial drug therapies (OR 0.55, 95% CI 0.49–0.62). However, one must mention that in rare cases, non-adherence to a harmful drug has actually protected patients participating in a trial from dying. This was the case during the investigation of antiarrhythmic drugs [15]. This clearly indicates that the impact of drug adherence on the incidence of minor or major side effects depends primarily on the quality of the drug under investigation.

Taken together, these observations suggest that drugs on the market are probably much more effective than we think, and that in clinical practice, the true efficacy of many drugs or treatment approaches is just diluted by the poor adherence pattern of some patients during the trials. Nevertheless for registration purposes, it would appear crucial to know what drugs are truly doing in terms of efficacy and safety, when they are taken correctly.

11.4 What Should Be Done to Improve the Actual Situation and to Integrate Adherence in Clinical Trials?

Today, adherence to therapy is still retaining little attention among trialists designing RCT. More attention remains focused on drop-out rates and pill count. Even when data on adherence are available, they are often handled inappropriately.

In order to further improve the quality of RCT and hence to strengthen the evidence gathered with these trials authors should:

(a) Implement at least one reliable method of measuring drug adherence, which enables to obtain a dosing history in the trial and consider the eventual limitations of the method.
(b) Present adherence data in all RCT with a distribution of the percentages of adherence in the various patients groups.

(c) Provide a clear definition of what they consider as inadequate adherence in the protocol.
(d) State in the protocol how data from patients who fulfill the criteria of inadequate compliance will be handled in the analysis of results.
(e) Provide a statistical plan including a percentage of non-adherence and drop-outs in the calculation of the power of the study.

Adding these important aspects in RCT will certainly contribute to improve their quality and the level of the evidence obtained from these studies before transferring the information into clinical practice. In addition, not overlooking one of the critical elements that affects the variability might have a huge impact on the cost of RCT. Indeed, non-adherence in clinical trials leads to enrolling more patients to reach endpoints, increases the study timeline and thus enhances operational costs. New technologies discussed in this book are being developed which will help organizers of clinical trials to obtain such information.

In conclusion, one can only cite the title of the paper written by Czobor and Skolnick [12],

"The secrets of a successful clinical trial: compliance, compliance, and compliance"

References

1. Masic I, Miokovic M, Muhamedagic B. Evidence based medicine—new approaches and challenges. Acta Inform Med. 2008;16(4):219–25.
2. van Onzenoort HA, Menger FE, Neef C, et al. Participation in a clinical trial enhances adherence and persistence to treatment: a retrospective cohort study. Hypertension. 2011;58(4):573–8.
3. Granger BB, Swedberg K, Ekman I, et al. Adherence to candesartan and placebo and outcomes in chronic heart failure in the CHARM programme: double-blind, randomised, controlled clinical trial. Lancet. 2005;366(9502):2005–11.
4. Simpson SH, Eurich DT, Majumdar SR, et al. A meta-analysis of the association between adherence to drug therapy and mortality. BMJ. 2006;333(7557):15.
5. Breckenridge A, Aronson JK, Blaschke TF, Hartman D, Peck CC, Vrijens B. Poor medication adherence in clinical trials: consequences and solutions. Nat Rev Drug Discov. 2017;16(3):149–50.
6. Blaschke TF, Osterberg L, Vrijens B, Urquhart J. Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories. Annu Rev Pharmacol Toxicol. 2012;52:275–301.
7. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. BMJ. 2008;336(7653):1114–7.
8. Pullar T, Kumar S, Feely M. Compliance in clinical trials. Ann Rheum Dis. 1989;48(10):871–5.
9. Gossec L, Tubach F, Dougados M, Ravaud P. Reporting of adherence to medication in recent randomized controlled trials of 6 chronic diseases: a systematic literature review. Am J Med Sci. 2007;334(4):248–54.
10. Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. N Engl J Med. 2015;372(6):509–18.

11. Investigators ET, Chertow GM, Block GA, et al. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. N Engl J Med. 2012;367(26):2482–94.
12. Czobor P, Skolnick P. The secrets of a successful clinical trial: compliance, compliance, and compliance. Mol Interv. 2011;11(2):107–10.
13. Kubo Y, Sterling LR, Parfrey PS, et al. Assessing the treatment effect in a randomized controlled trial with extensive non-adherence: the EVOLVE trial. Pharm Stat. 2015;14(4):368.
14. Beaussier H, Boutouyrie P, Bobrie G, et al. True antihypertensive efficacy of sequential nephron blockade in patients with resistant hypertension and confirmed medication adherence. J Hypertens. 2015;33(12):2526–33.
15. Bobrie G, Frank M, Azizi M, et al. Sequential nephron blockade versus sequential renin-angiotensin system blockade in resistant hypertension: a prospective, randomized, open blinded endpoint study. J Hypertens. 2012;30(8):1656–64.
16. Bhatt DL, Kandzari DE, O'Neill WW, et al. A controlled trial of renal denervation for resistant hypertension. N Engl J Med. 2014;370(15):1393–401.

The Impact of Antihypertensive Drugs on Adherence

12

Ian M. Kronish and Nathalie Moise

12.1 Introduction

In the first half of the twentieth century, experts debated whether hypertension represented a true cardiovascular risk factor that required treatment or was simply a benign component of aging [1]. At the time, there were few evidence-based treatments for hypertension. For those with malignant hypertension, the only proven treatment was a sympathectomy, an invasive procedure with high potential for surgical complications and postoperative adverse effects including hypotension [2]. In the 1950s, the first new generation of antihypertensive drugs with proven blood pressure lowering effects was discovered. These included phenoxybenzamine, a sympathetic nerve blocker, hexamethonium, a ganglion blocker, and guanethidine, a peripheral adrenergic inhibitor. These early drug classes effectively reduced blood pressure, but produced substantial side effects, most notably orthostatic hypotension and syncope. The next major advance was the discovery of reserpine, the active alkaloid in the plant Rauwolfia serpentina. Reserpine lowers blood pressure by preventing the release of catecholamines by peripheral sympathetic nervous system neurons [3]. However, this medication also produced potentially serious patient reported side effects including fatigue, insomnia, depression, Parkinson's-like symptoms as well as hypotension and bradycardia [3]. The 1950s also saw the discovery of hydralazine, a vasodilator that effectively reduces blood pressure but whose use has been limited by its short half-life, requiring multiple doses per day, and symptomatic side effects such as headaches and palpitations. Not surprisingly, adherence to these early antihypertensive medications was poor.

I. M. Kronish, M.D., M.P.H. (✉) · N. Moise, M.D., M.S.
Center for Behavioral Cardiovascular Health, Columbia University Medical Center, New York, NY, USA
e-mail: ik2293@columbia.edu; ik2293@cumc.columbia.edu; nm2562@cumc.columbia.edu

M. Burnier (ed.), *Drug Adherence in Hypertension and Cardiovascular Protection*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-76593-8_12

Table 12.1 Antihypertensive drug classes and mechanism of action

Antihypertensive drug class	Mechanism of action	Example
Thiazide or thiazide-like diuretics	Promote endothelial or vascular smooth muscle-mediated vasodilation, decreased sodium reabsorption, and decreased extracellular volume	Chlorthalidone
Potassium-sparing diuretics	Interfere with sodium-potassium exchange at the distal convoluted tubule of the kidney	Amiloride/ triamterene
Aldosterone antagonists	Compete with aldosterone receptor sites thus blocking sodium/water retention by the renal tubules	Spironolactone
Loop diuretics	Inhibit reabsorption of sodium and chloride by renal tubules	Furosemide
Beta-blockers	Block beta receptors in the heart and peripheral circulatory system which leads to decrease in cardiac output, renin release, sympathetic nervous systemic activity; intraclass differences are determined by lipid/water solubility, cardio-selectivity, and vasodilatory properties	Metoprolol
Angiotensive converting enzyme inhibitors (ACEI)	Inhibit angiotensin converting enzyme conversion of angiotensin I to angiotensin II, a potent vasoconstrictor that also stimulates the release of aldosterone, a promoter of sodium retention	Lisinopril
Angiotensin II receptor blockers (ARBs)	Blocks angiotensin II receptor, and thus prevents the action of angiotensin II, a potent vasoconstrictor that stimulates the release of aldosterone	Losartan
Direct renin inhibitors (DRI)	Decrease renin activity and inhibit conversion of angiotensinogen to angiotensin I, thus decreasing angiotensin II as well	Aliskiren
Calcium channel blockers (CCBs)	Block influx of calcium ion into vascular smooth muscle and myocardium; intraclass differences result in differential selectivity for myocardial versus peripheral arterial effects	Amlodipine
Alpha-1 blockers	Block postsynaptic alpha1-adrenergic receptor, which leads to dilation of peripheral arterioles and veins	Prazosin
Alpha-2 receptor agonists	Stimulate presynaptic alpha2-adrenergic receptors in the brain, which reduces sympathetic nervous activity	Clonidine
Combined alpha- and beta-receptor blockers	Block both alpha and beta receptors to produce combined effects of blocking both receptors	Carvedilol
Central agonists	Stimulates inhibitory adrenoreceptors in the brain which reduces sympathetic nervous activity from the brain	Methyldopa
Peripheral adrenergic blockers	Depletes adrenergic amines which prevents peripheral smooth muscle from receiving message to vasoconstrict resulting instead in vasodilation	Reserpine
Vasodilators	Relax blood vessels to improve blood flow	Hydralazine

The modern era of antihypertensive medications was heralded by the discovery of the thiazide diuretic chlorothiazide in 1957. Since then, there has been a remarkable increase in the number of medications that are considered safe and well tolerated in the treatment of hypertension. Overall, there are currently 14 classes of antihypertensive medications, covered by approximately 100 distinct medications, some of which represent combinations of drug classes (Table 12.1). The expansion

of drug classes saw a concomitant evolution, predominantly led by the Joint National Committee, in the definition of hypertension from one based on elevated diastolic blood pressure to increased focus on elevated systolic blood pressure. At the same time, there was an accumulation of evidence demonstrating the benefits of lowering blood pressure to prevent cardiovascular disease [4]. The strengthened evidence for a relationship between treatment and cardiovascular risk reduction increased the importance of achieving blood pressure control, and increased the proportion of patients prescribed multiple antihypertensive medications chronically.

Despite the development of many well-tolerated medications, nonadherence to antihypertensive medications has remained high. In fact, persistence with antihypertensive therapy at 4 years is estimated to be only 46% in patients with established hypertension and 78% in patients with newly diagnosed hypertension [5–9]. Even patients refilling their medications have challenges taking their medications on a daily basis. This has prompted a long-standing and growing interest in understanding the etiology of nonadherence to antihypertensive medications. While the reasons for nonadherence are multifactorial, the literature has consistently shown that even with the discovery of better tolerated medications, specific characteristics of antihypertensive medications continue to play an important role in nonadherence.

The goal of this chapter is to increase the understanding of the impact of drug characteristics on adherence to antihypertensive medications. We begin by broadly describing the mechanisms by which characteristics of antihypertensive drugs impact adherence. We next describe common adverse effects of specific antihypertensive drugs that impact adherence, focusing on drugs from the classes recommended as first line in United States and other international guidelines. We next review the epidemiologic literature demonstrating an association between antihypertensive drug class and adherence. We conclude by suggesting approaches to preventing and overcoming the potential adverse impact of antihypertensive drugs on adherence.

12.2 Defining and Measuring Adherence

Before describing the associations between antihypertensive drugs and adherence, it is important to provide a framework for defining nonadherence. Adherence is generally defined as the extent to which a patient follows the regimen as recommended by their clinicians [5, 10]. In this chapter, we follow the taxonomy of adherence behaviors recommended by Vrijens and colleagues as part of a European consensus building project [11]. These behaviors encompass: (1) initiation of the drug regimen which typically requires filling a medication at a pharmacy; (2) day-to-day implementation of the regimen including taking individual pills at the prescribed timing and with the proper technique (e.g., with or without food); and (3) persistence with the regimen by obtaining medication refills. It is worth noting that antihypertensive drugs may exert differential effects on these adherence behaviors. For example, drugs with high out-of-pocket costs may have lower rates of treatment initiation (also known as primary nonadherence). However, once initiated, such drugs might be easily implemented, and thus taken regularly on a day-to-day basis.

Drugs with complex dosing regimens, in contrast, might have similar treatment initiation rates compared to drugs with easy once-per-day dosing, but lower day-to-day implementation of the regimen due to challenges following a complex regimen. Similarly, drugs with a higher frequency of serious adverse effects may have similar rates of treatment initiation as compared to better tolerated drugs, but greater premature discontinuation when adverse effects ensue.

12.3 Mechanisms by Which Antihypertensive Characteristics Can Impact Adherence

In this section, we provide a list of mechanisms that explain how different aspects of antihypertensive drugs can impact medication adherence (Table 12.2). A key concept is the notion of tolerability. Tolerability refers to the degree to which adverse drug effects are tolerated by individuals [12]. Since the first studies demonstrated that tolerability of drugs was an important factor in adherence, a number of investigators have posited that differences in the adverse effects of antihypertensives may underlie differences in adherence by drug class or in adherence between drugs within the same class. Side effects and other adverse drug effects greatly impact the tolerability of a drug. The affordability of a drug also plays a role, and hence, out-of-pocket costs should also be considered. Other factors described below pertain to dosing complexity, physical properties of drugs, and perceptions of harms and benefits of individual drugs or drug classes irrespective as to whether these are confirmed through personal experience.

Symptomatic Side Effects: Side effects, defined here as unintended medication effects that occur at regular doses, are commonly experienced with antihypertensives

Table 12.2 Antihypertensive properties and impact on adherence

Antihypertensive property	Impact on adherence
Symptomatic side effects	Adverse side effects experienced by patients may increase skipped doses and hasten premature treatment discontinuation
Other adverse effects (e.g., electrolyte abnormalities, hyperglycemia)	Asymptomatic adverse drug effects may increase patient or physician discontinuation. The need for additional testing (e.g., blood tests for electrolyte monitoring) to monitor for these adverse drug effects may also promote nonadherence
Out-of-pocket cost	High drug costs may increase primary nonadherence (i.e., failure to ever fill a first prescription) and refill adherence, leading patients to stretch the time between fills
Dosing complexity	Simple, flexible dosing regimens that are once per day may have superior adherence compared to complex multi-dose per day regimens
Physical properties of drug	The size, shape, or color of a drug can affect medication-taking patterns
Perceived effectiveness	Drugs that are perceived to be effective by providers or patients, whether due to evidence-based data, expert opinion, or marketing, may lead to greater adherence

[13]. Overall, the proportion of patients who experience symptomatic side effects due to antihypertensives ranges from 20 to 97% [14]. Older individuals are generally more vulnerable to side effects due to physiological and pathological factors that impact how the body handles a drug [12]. Medical comorbidities that affect the pharmacokinetics and pharmacodynamics of medications, such as renal and cardiac dysfunction, can also increase risk for side effects. In addition, regimen complexity can increase risk for side effects through drug–drug interactions. Multiple studies have confirmed that symptomatic side effects increase risk for medication nonadherence. For example, Morgado and colleagues found that individuals who reported having one or more side effect symptoms were 3.7 times more likely to self-report being nonadherent at that time than individuals with no symptoms [15]. Tedla and colleagues sought to better understand the way side effects impacted adherence by grouping symptoms related to antihypertensive medications into clusters using the Physical Symptoms Distress Index [16]. The authors learned that 86% of participants experienced at least one drug-related side effect. Interestingly, only the genitourinary symptoms cluster was significantly associated with a pill count measure of adherence; those with at least one genitourinary symptom (particularly excessive urination or decreased sexual drive) had a 7.1% lower adherence compared to those with no symptoms.

Other Adverse Effects. Antihypertensive drugs also lead to adverse effects that do not reliably produce symptoms. These adverse effects may lead clinicians to discontinue medications. Strictly speaking, discontinuation of medications when recommended by clinicians does not represent nonadherence. That said, patient concerns about these adverse effects can adversely impact adherence. Moreover, the experience of the adverse effects may lead patients to become less trusting of future prescribed medications. Monitoring requirements for these adverse effects through frequent blood tests, for example, may also increase the "work" of taking antihypertensives, which may in turn adversely impact adherence. Accordingly, clinicians are encouraged to select antihypertensive medications with the lowest risks of resulting in adverse effects.

Cost. Differences in out-of-pocket costs for antihypertensives may also impact adherence, particularly in lower-income patient populations for whom even small costs can be difficult to bear. In one systematic review that identified 24 unique studies of the association between medication cost and adherence, 75% of the studies showed a significant relationship between increased patient cost-sharing and nonadherence [17]. Steinman et al. (2001) demonstrated that among seniors, medication restriction because of cost was associated with lack of prescription coverage, as well as low-income out-of-pocket drug costs [18]. One value-based insurance design program that eliminated generic medication copayments and reduced brand name copayments found improvement in medication possession ratios for all medication classes except ARBs, which did not have generic equivalents available at that time [19]. However, since the publication of this study, ARBs have become generic, lessening concerns about cost-related nonadherence for this class of medication. It might be present, however, for other drugs without generic alternatives available, such as the current class of direct renin inhibitors. Thus, out-of-pocket costs can

vary according to the availability of generic drugs as well as the specifics of formularies and the insurance status of patients. As such, the effect of cost on adherence often represents the intersection both drug and patient characteristics.

Dosing Complexity: Multiple studies have shown that regimen complexity may affect adherence to antihypertensive medications. A systematic review showed modestly greater refill adherence to once-a-day formulations (91.4%) compared to twice a day formulations (87.1%) and more than twice per day (86.3%) formulations [20].

Physical Properties: The color, size, and shape of pills can influence adherence. In the case of antihypertensives [21, 22], Lumbreras and Lopez-Pintor compared self-reported adherence to angiotensin receptor blockers after switches in the physical characteristics of the pills, which commonly occurred in Spain soon after generic substitutions for brand name ARBs became available [23]. The authors confirmed that adherence was lower among patients who had experienced switches in pill appearance.

Perceived Benefits and Harms: Medication adherence is shaped, in part, by perceptions of benefits of harms [24, 25]. Typically, these beliefs influence adherence antihypertensives equally, without differences between specific drugs. Marketing for specific antihypertensives, and general preferences for newer brand names medications, however, may lead to differences in perceived benefits and harms of specific antihypertensive medications. Interestingly, despite direct-to-consumer advertising, most patients have positive perceptions of generic medications [26]. In fact, among 101,618 hypertensive patients in Italy initiating monotherapy with generic versus brand name antihypertensive medications, discontinuation rates were similar after adjustment for demographic and clinical factors [27]. Another study that occurred during the introduction of generic ramipril to the market, found that adherence was slightly higher for generic than brand name ramipril [28]. Patients may also gain different perceptions for specific antihypertensive medications or medication classes through word-of-mouth experiences from family members or friends, as well as through direct experiences.

12.4 Properties of Antihypertensive Drug Classes Relevant to Adherence

While the side effects of newer antihypertensive agents are generally lower in frequency and severity compared to the earlier nerve-blocking antihypertensive agents, even the newest medications continue to present a range of both symptomatic and asymptomatic adverse effects, and nonadherence remains suboptimal. Medication adherence remains a key determinant of blood pressure control [29–31]. In this section, we described the pharmacologic properties of the commonly prescribed antihypertensive drug classes that might impact adherence. These clinically significant differences in drug pharmacology may lead to differences in side effects and thus tolerability from a patient's perspective. Understanding these properties may help

clinicians personalize the selection of antihypertensives and be vigilant for adverse effects that could lead to nonadherence or early discontinuation.

Currently, most guidelines including the Joint National Committee (JNC) 8 [32], American Society of Hypertension/International Society of Hypertension [33], and the European Society of Hypertension/European Society of Cardiology [34] recommend that the initial antihypertensive drug be selected from one of four classes: thiazide diuretics, CCBs, ACEIs, and ARBs. The selection of these classes was generally based on evidence from randomized control trials comparing individual drug classes to one another or placebo. Accordingly, we focus our review of properties of antihypertensives to medications within these four drug classes. As the majority of patients require two or more medications to achieve tight blood pressure control, we additionally describe the relevant drug properties associated with commonly used second-line antihypertensives.

Thiazide diuretics. The mechanisms of action by which thiazide diuretics lower blood pressure are poorly understood, and are thought to relate to endothelial or vascular smooth muscle-mediated vasodilation, decreased sodium absorption in the distal renal tubules, decreased extracellular volume which in turn produces a decline in volume, diminished venous return, and eventually lower cardiac output and blood pressure [35]. In some (e.g., JNC-7), but not all guidelines, thiazide diuretics are recommended as the preferred first-line medication. This recommendation is primarily based on the findings of the landmark Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), which showed that the thiazide-like diuretic chlorthalidone was more effective than amlodipine (a CCB), lisinopril (an ACEI), and doxazosin (an alpha-blocker) for reducing cardiovascular morbidity and mortality [36]. From an adherence point of view, thiazide diuretics have several advantages: (1) they are typically prescribed once a day and (2) certain thiazides, most notably chlorthalidone, have a relatively long half-life such that occasional missed doses will have a small impact on drug levels, and hence on BP control, a concept known as "forgiveness" [37]. Thiazide diuretics also have properties that can negatively influence adherence. To begin with, a common side effect, particularly when initiated, is increased urination. In theory, this symptom should resolve with regular use, but intermittent non-adherers may be particularly susceptible to this side effect. Other concerns are related to increased risk of erectile dysfunction in men. As described above, genitourinary side effects may have a particular adverse effect on adherence. Overall, individuals taking diuretics are more likely to experience side effects than those taking other antihypertensive drugs [38]. Thiazide diuretics can also lead to electrolyte abnormalities such as hypokalemia, glucose intolerance, hyperlipidemia, and hyperuricemia (a setup for gout flares). Among older adults, one study suggested that chlorthalidone as compared to other thiazide diuretics is associated with increased electrolyte abnormalities without a superior benefit with respect to cardiovascular outcomes [39]. These metabolic and electrolyte side effects may lead to a clinical indication for routine monitoring via blood testing, particularly in older adults, that may be undesirable for patients and could foster discontinuation by patients or clinicians [40].

CCBs: CCBs mechanism of action is through blocking the influx of calcium ions into vascular smooth muscle. They can be categorized into three groups: (1) dihydropyridinic agents, the most widely used CCBs for hypertension which act as dilating agents at peripheral vessel level; (2) phenilalchilaminic agents, which predominantly act as negative inotropes and chronotropes at the cardiac level; and (3) benzothiazepinic agents, which have an intermediate profile. The advantage of CCBs as compared to the other first-line antihypertensives, is that they uncommonly result in electrolyte abnormalities and do not require any special monitoring via blood tests. The most common side effects of the dihidropyridines relate to their vasodilatory effects, potentially resulting in peripheral edema, headaches, and flushing [41]. The edema is not typically responsive to diuretic medications. The principal side effects of the non-dihidropyridines relate to their chronotropic effects, and include conduction delays and bradycardia. Constipation is especially common with verapamil, one of the non-dihidropyridines. When considering these agents, physicians should be aware that the side effects of CCBs are typically dose dependent.

ACEI and ARBs. ACEIs and ARBs both block the renin-angiotensin aldosterone system. ACEIs produce vasodilation by inhibiting the formation of angiotensin II (a vasoconstrictor), thus promoting excretion of sodium and water by blocking the effects of angiotensin II in the kidney as well as inhibiting cardiac and vascular remodeling. ARBs are receptor antagonists that block type I angiotensin II receptors on blood vessels and other tissues, such as the heart, and thus also have natriuretic, diuretic, and cardiac remodeling effects. Historically, ACEIs were shown to improve outcomes in patients with left ventricular dysfunction, heart failure, or prior myocardial infarction. The Heart Outcomes Prevention Evaluation Study (HOPE) found that patients at high risk for cardiovascular disease, irrespective of underlying hypertension, had reduced cardiovascular morbidity and mortality on ramipril compared to placebos; given the small difference in BP reduction, the authors suggested protective mechanisms related to direct effects on the heart or vascular [42]. To the extent that clinicians and patients are aware of the findings of this landmark trial, perceptions of increased benefit for this drug may positively influence adherence. The properties of ACEIs and ARBs can also explain the side effects seen in these medications. ACEIs also block the breakdown of bradykinin (a vasodilator substance) that is thought to be responsible for a dry cough that occurs in up to 10% of patients [43]. Fortunately, the effect typically resolves within days of discontinuing the agent. The HOPE trial demonstrated that patients in the ramipril (ACEI) (vs. placebo) group were more likely to discontinue treatment due to cough (7.3% vs. 1.8%) or hypotension/dizziness (1.9% vs. 1.5%). Angioedema has also been reported in individuals taking ACEIs, likely related to the kallikrein-kinin system, and is higher among African-Americans [44, 45]. One community-based trial found that ARBs, which do not directly influence bradykinin, are less likely to cause cough and are better tolerated than ACEIs [46].

Beta-Blockers (BB). BB have been used to treat hypertension for decades, and have been relegated to second-line agents in some recent hypertension guidelines, unless there are compelling indications for BBs as first line, such as underlying

coronary heart disease, congestive heart failure, migraine prophylaxis, or for heart rate control. BBs decrease cardiac output, renin release, and sympathetic nervous systemic activity among other effects [12]. In 2004, Carlberg and colleagues published a systematic review demonstrating that atenolol may produce a smaller reduction in mortality compared to other hypertension classes [47]. This study and subsequent studies contributed to relegating BB to second-line treatment. Common side effects of BBs include bradycardia and insulin sensitivity [12]. While second-generation BBs (e.g., atenolol, metoprolol) are more selective for the beta-1 adrenergic receptor than first-line BBs (e.g., propranolol) that act on beta-1 and beta-2 receptors, third-generation drugs, also known as combined alpha and beta-blockers (e.g., carvedilol), have vasodilatory effects and, generally, improved tolerability [48]. One systematic review found that nebivolol, a highly selective beta-1 adrenergic receptor blocker, had similar tolerability to placebo and higher tolerability than other BBs, CCBs (nifedipine), and ARBs [49]. Although many once-per-day formulations are now available, many BBs were initially only available as multi-day dosing formulations, which as described above, could contribute to lower adherence.

Other agents: Other second line antihypertensive medications are still commonly used in patients with intolerances to first-line medications or in those with treatment resistant hypertension, requiring three or more medications. Centrally acting agonists, such as clonidine, stimulate alpha receptors in the brain, can induce psychological effects including depression and hallucinations. Individuals who are intermittently nonadherent to clonidine are susceptible to hypertensive crisis after abrupt withdrawal. Alpha-blockers have modest blood pressure lowering effects, and are no longer recommended as first line since the publication of the ALLHAT trial, showing inferior cardiovascular risk reduction. They may be useful, however, in men with concomitant benign prostatic hypertrophy. Common adverse effects include dizziness, orthostatic hypotension, and syncope. Aldosterone antagonists are increasingly recommended in treatment resistant hypertension, even in patients without biochemical evidence of hyperaldosteronism, a relatively common cause of identifiable hypertension [50]. The use of this class of medications is commonly limited by the potential for hyperkalemia. They can also be limited by symptoms such as breast tenderness and gynecomastia, particularly in men. A switch to more selective agents (e.g., eplerenone) in this class can reduce the incidence of these endocrine system side effects. Hydralazine, one of the first antihypertensives approved by the Food and Drug Administration, is still used in those with severe or resistant hypertension. It causes direct relaxation of arteriolar and smooth muscles. Advantages include fewer electrolyte abnormalities necessitating blood monitoring as compared to some other second-line medications like aldosterone antagonists. Hydralazine, however can produce serious side effects including a lupus-like syndrome in 10–20% of patients, tachycardia, headache, dizziness, flushing, and myocardial ischemia; combining this drug with a diuretic and BB can prevent side effects such as fluid retention and tachycardia, respectively [50]. Newer direct renin inhibitors (DRIs), which inhibit renin-angiotensin aldosterone system, are increasingly being evaluated. A systematic review demonstrated that mean event rates of dizziness and headaches appeared to be slightly higher in the DRI group (6.0 and

10%) compared to ACEIs (4.4 and 7.9%) and ARBs (3.7 and 6.3%) [51]. The most common side effects are gastrointestinal, particularly in women and the elderly [52], which, along with cost, may adversely impact adherence.

12.5 Evidence for an Association Between Antihypertensive Drug Class and Adherence

Thus far, we have described mechanisms and drug properties that explain how antihypertensive drugs can impact adherence. In this section, we will review the epidemiological evidence for these associations. Initial evidence for the impact of antihypertensive drug class on adherence can be drawn from prior randomized clinical trials comparing the effects of different classes of antihypertensives. The primary aim of the majority of these trials was to compare the effects of antihypertensive drugs on blood pressure, but some also assessed adherence as a secondary outcome. Most notably, in the ALLHAT, persistence with treatment at 1 year, one measure of adherence, ranged from 83% for lisinopril (ACEI) to 88% for amlodipine (CCB) [36]. The Losartan Intervention For Endpoint reduction in hypertension study (LIFE) trial found higher persistence (i.e., less dropout due to adverse event) for losartan (ARB) (87%) than atenolol (BB) (83%) [53]. The Heart Outcomes Prevention Evaluation Study (HOPE) found persistence rates for ramipril were 87% at 1 year, 85% at 2 years, 82% at 3 years, and 75% at 4 years [54]. Overall, when examining data from these clinical trials, it appears as though persistence with all antihypertensive drug classes is fairly high and as if there are not major differences between drug classes. Yet, as a result of selection bias, run-in periods, behavior reinforcement through close follow-up, and lack of out-of-pocket costs, adherence to medications in clinical trial settings may not be representative of adherence in the "real world." Moreover, the aforementioned trials did not rigorously assess how well the regimen was implemented on a day-to-day basis, and hence, provide a limited understanding of the expected effects of antihypertensives on the full spectrum of adherence behaviors in routine clinical practice.

We have to turn to observational studies to gain a better understanding of the population-level effect of drugs on adherence [55]. To better understand the impact of antihypertensive drug class on adherence in clinical settings, Kronish and colleagues (2011) performed a meta-analysis of studies up to 2009 assessing the association between drug class and two definitions of adherence to antihypertensive medications, persistence and day-to-day implementation [56]. The systematic search yielded 17 unique articles for 935,920 patients. The included studies relied upon medication refill data from insurance claims or pharmacy refills data. The pooled mean persistence with medication was highest for ARBs (65%) compared to other drug classes studied (ACEI, 58%, CCB, 52%, diuretics, 51%, BB, 28%). The authors also noted that after accounting for publication bias, the differences between ARBs and ACEIs as well as diuretics and BBs were no longer significant. Overall, when compared to patients prescribed diuretics and BBs, the drug classes associated with the lowest adherence, patients prescribed ARBs had approximately twice the odds of

having good adherence, with ACEIs appearing to have the second best level of adherence, followed by CCBs. A higher frequency of side effects, both asymptomatic and symptomatic ones, with thiazide diuretics and BBs could have explained the differences in adherence by drug class observed in the meta-analysis.

Since the publication of this meta-analysis in 2011, several other important studies of the association between drug class and adherence have been reported. Ritchey and colleagues assessed the association between demographic characteristics and adherence to antihypertensives among 18.5 million Medicare advantage and medication fee-for-service beneficiaries aged 65 years with Medicare Part D prescription coverage during 2014 [57]. Beneficiaries were categorized as nonadherent if the proportion of days covered (PDC) with each drug was less than 80%, a commonly used cutpoint. Consistent with the Kronish meta-analysis, they learned that there were again significant differences in adherence by drug class, with adherence highest for ACEIs and ARBs and lowest for a mixed group of antihypertensives (selective aldosterone receptor inhibitors, peripheral vasodilators, alpha-blockers, and centrally acting agents) and diuretics (Table 12.3). However, among this more uniform patient population, there was only a 10% difference in the proportion adherent between the best (ARB, 83%) and worst (thiazide diuretic, 73%) first-line drug class. These data suggest that, at least among older adults with Medicare Part D coverage, drug class does not have a large impact on adherence.

Tajeu and colleagues similarly examined the trends in adherence to antihypertensive in Medicare beneficiaries from 2007 to 2012, and again found that discontinuation was most likely with non-first line antihypertensive classes (e.g., BBs and loop diuretics) and least likely with ACEIs and ARBs [58]. In contrast, when adherence was measured using a PDC < 80%, the pattern of association between drug class and adherence was somewhat different. The most significant change was that although ARBs were in the group least associated with discontinuation, they were among the drug classes most associated with low adherence. These data support the hypothesis that drug class can exert different effects on different aspects of adherence behavior.

While the prior studies were limited to Medicare beneficiaries in the United States, these patterns of associations between drug class and adherence have also been observed in international settings. In the meta-analysis by Kronish and

Table 12.3 Association between drug class and nonadherence, adapted from Ritchey et al. [57]

Antihypertensive medication class	N of beneficiaries	N of fills (millions)	Out-of-pocket spending per beneficiary ($)	% nonadherent
Angiotensin receptor blocker	4,890,687	29.7	98	16.9
Angiotensin converting enzyme inhibitor	7,411,281	42.0	30	18.5
Calcium channel blocker	7,144,600	40.5	49	22.9
Beta-blocker	9,645,375	54.3	48	23.4
Thiazide diuretic	6,874,909	35.1	39	27.2
Other	1,847,807	10.4	42	35.9

colleagues, cohorts came from multiple continents (North America and Europe) and settings. The country of the study did not change the pattern of association between drug class and adherence in this meta-analysis. A more recent study in Asia (South Korea) found a similar pattern of the influence of drug class on adherence [59].

While the preponderance of data suggests that there are significant differences in adherence by drug class [60], it is worth noting that this pattern has not been found in all samples. In a more recent study using a Swedish Primary Care cardiovascular database, there were not differences in drug persistence by drug class, including for diuretics versus other antihypertensive drug classes [61]. Of note, this sample was not limited to elderly adults, a group more susceptible to side effects, as the US Medicare samples were.

While most large studies of the impact of antihypertensive drugs on adherence have examined difference in adherence by drug class, there are some studies that have examined differences within drug classes. For example, Choi and colleagues compared adherence between atenolol, an older beta-blocker, and newer generation beta-blockers [62]. They found that some of the newer generation medications, most notably carvedilol, had a lower hazard of discontinuation. Whether these differences have more to do with selection factors or with the increased branding and marketing of such drugs versus true differences in side effects is unclear.

Others have examined the relationship between drug class and adherence using adherence measurement techniques other than pharmacy fill data. Refill patterns measure whether a patient presents to a pharmacy regularly to retrieve their medications, but does not account for missed or skipped daily doses. Moise and colleagues (2015) assessed adherence in 149 persistently uncontrolled hypertensive primary care patients using electronic pillboxes, which measure mean day-to-day adherence, between two office visits [63]. Adherence was lowest for BBs (70.9%) compared to ARBs (75.0%, $P = 0.11$), diuretics (75.9%, $P < 0.001$), CCBs (77.6%, $P < 0.001$), and ACEIs (78.0%, $P < 0.0001$). However, in adjusted analyses, dosing frequency but not drug class was related to electronically measured adherence, suggesting that differences in adherence attributed to BBs were due to the fact that they were more likely to be prescribed as twice a day formulations [63]. It is worth noting, however, that these observed between-class differences in day-to-day implementation were relatively small, and on average, drug class did not have a large impact on typical adherence among patients with predominantly multi-drug regimens.

12.6 Heterogeneity of Treatment Effects and N-of-1 Trials

Thus far, we have considered population-level effects of drugs on the typical or "average" patient. In reality, there are heterogeneous treatment effects between patients. That is, the same drug might have no side effects in some patients, but severe side effects in another. In fact, there are substantial inter-individual

differences in the effects of antihypertensive medications [64–67]. For example, in a study of 56 hypertensive patients who received one of four antihypertensive medications from distinct drug classes, 39% of patients achieved controlled blood pressure on a first, randomly selected medication [64]. However, after systematically assessing the response to each of the four medications, nearly twice as many patients (73%) achieved controlled blood pressure on a single medication. Scientists have examined whether gene polymorphisms or hormone tests can predict which antihypertensive medication will be most effective for individual patients [68], but reliable predictors have yet to be identified [69]. The field of pharmacogenomics has similarly been searching for reliable predictors of person-specific side effects. Unfortunately, thus far, we do not have reliable tests to determine which patient is going to have the adverse effect or the best blood pressure lowering effect.

Since there are no proven patient characteristics or tests to predict with sufficient accuracy how individual patients will respond to individual antihypertensive medications, clinicians have relied upon the unsystematic and potentially harmful "trial of therapy" approach (i.e., trying a medication in an unsystematic way until proven inefficacious or harmful) [70]. N-of-1 trials are experiments conducted by individual patients [71] and offer an intriguing approach to increasing the precision of blood pressure treatment. Although there are various N-of-1 trial designs, a commonality is that patients compare multiple treatments using a multiple crossover design with rigorous monitoring for treatment effects (both benefits and harms) that are most important to patients and clinicians [72–76]. With recent innovations in mobile health technology, N-of-1 trials may become more feasible to implement. In the foreseeable future, smartphones could be used to host an N-of-1 trial application ("app"), which guides patients through the trial, reminds them which treatments they should take and when, and enables them to complete electronic side effect diaries that are less cumbersome than paper-and-pen ones [77]. Wireless home blood pressure monitors can also now remotely capture blood pressure data, and algorithms for data analysis and visualization can be programmed into an N-of-1 "app."

N-of-1 trials are postulated to improve clinical outcomes by increasing satisfaction with treatment, and in turn, improving medication adherence and clinical outcomes. Accumulating evidence suggests that when operational complexities can be overcome, patients benefit from N-of-1 trials. N-of-1 trials for conditions other than hypertension (e.g., chronic pain and asthma) have reported that 79% of patients participating in them find them useful [78], up to 65% of patients change treatment as a result of their involvement [79], and 84–100% continue therapy consistent with N-of-1 trial results [79, 80]. Participation in N-of-1 trials can also increase patients' understanding of and increase their sense of control over their chronic disease [81], factors that can improve adherence to treatment. Despite the potential benefit of applying N-of-1 trials to hypertension, the effect of N-of-1 trials of blood pressure medications on patient-centered outcomes is just beginning to be tested in several ongoing trials. Whether this approach can truly help optimize adherence through more precise treatment selection remains to be seen.

12.7 Approaches to Minimizing Nonadherence Due to Drug Class

There are other more established approaches to optimizing the selection of blood pressure medications in a manner that will minimize the risk of nonadherence. The Center for Disease Control's (CDC) Million Hearts Initiative recommends the SIMPLE method of Simplifying the regimen, Imparting knowledge, Modifying beliefs and behavior through reinforcement, Providing communication and trust, Leaving the bias (e.g., by understanding the predictors of nonadherence), and Evaluating adherence through validated scales (http://www.acpm.org/?MedAdhereTTProviders). Below we review some recommendations for improving nonadherence, particularly due to drug class-related mechanisms such as symptomatic side effects and other adverse effects.

Communication: Poor provider communication about side effects at the time of prescribing may contribute to nonadherence. In fact, providers address adverse effects only 35% of the time, and explain the pill number and frequency, and timing only about half of the time [82]. Experts continue to recommend that providers identify barriers to adherence when prescribing medications and seek to involve patients in decision-making as a means to improving adherence [83], particularly as it relates to differences in drug classes. Shared decision-making (SDM) refers to a collaborative process whereby clinicians and patients make health decisions together by exchanging information about the best available evidence and taking patients' preferences and values into account. Published studies show that patients prefer to be involved in treatment decisions, and interventions that enhance shared decision-making enhance treatment adherence and satisfaction [84, 85]. With respect to minimizing nonadherence related to drug effects, a clinician might describe side effects of different drug classes and seek input about which drug the patient would prefer to initiate. However, it can be argued that this approach may risk inducing a nocebo effect, biasing patients to experience and thus report specific side effects, and worsening adherence rates. It remains unknown which approach to addressing potential side effects would best reduce adverse effects of drugs on adherence.

Minimizing out-of-pocket costs: One value-based insurance design program that eliminated generic medication copayments and reduced brand name copayments found improvement in medication possession ratios for ACEIs, BBs, CCBs, though not ARBs, which did not have generic equivalents available at that time [19]. The results of this study serve as a reminder that clinicians should be mindful to inquire about trouble affording medications due to cost, typically favoring generic medications with low out-of-pocket costs over brand name ones, particularly in the area of hypertension with so many generic medications available.

Lifestyle recommendations: Some prior data has shown that a healthy lifestyle can decrease the risk of medication side effects. Accordingly, Dharmarajan and Dharmarajan (2015) posit that the key to successful therapy and tolerability is

to promote a healthy lifestyle (i.e., diet and exercise) in conjunction with medications [12].

Keep the regimen simple: Fixed combinations in particular may improve adherence. One study found that fixed combinations that included diuretics (a drug class particularly associated with low adherence) showed a 19.8% lower chance for nonadherence compared to diuretic monotherapies, suggesting that combination drugs may mitigate drug class effects on nonadherence [60]. A systematic review found that compared to placebo, polypills are effective in reducing blood pressure, and while there were slightly higher discontinuation rates, reported adverse events were similar [86]. As the aforementioned data relating to adherence to BBs in patients with uncontrolled hypertension revealed, favoring extended release, once-per-day formulations over multi-day dosings is also likely to be beneficial to adherence [63].

Routinely assess side effects and adherence: Given the high prevalence of side effects and nonadherence, clinicians are encouraged to routinely inquire about side effects and adherence in a non-judgmental manner. When nonadherence is suspected, clinicians should explore the reasons for nonadherence, including cost and perceived side effects. Clinicians can then incorporate behavior-change techniques from effective, multicomponent interventions into their practice [87]. When the reasons for nonadherence pertain to effects of the drug such as cost or side effects, then switching to an alternative medication may be appropriate.

Conclusions

The preponderance of evidence suggests that there are population-level differences in adherence by drug class. Among the four first-line classes, there appears to be lower adherence to thiazide diuretics and higher adherence to ARBs and ACEIs, particularly in older adults. Whether these differences in adherence are sufficient to result in differences in blood pressure control is not proven, but clinicians might consider these differences as one factor when deciding on first-line drug treatment, particularly among patients that have a track-record of nonadherence or sensitivity to side effects.

Perhaps more important than the population-level differences in adherence by drug level are the inter-individual-level differences in which some patients are expected to have severe side effects or toxicities to certain drug classes but not to others. This suggests the importance of careful follow-up of patients. N-of-1 trials offer an exciting potential new approach to prescribing in which patients get to gain direct evidence as to the relative benefits and harms of multiple classes of blood pressure medications. Such knowledge may be helpful to sustaining long-term adherence. This approach, however, requires a patient to be engaged in self-monitoring for an extended period of time. Whether such an approach will play a substantial role in the clinical management of hypertension remains to be seen, and several ongoing clinical trials promise to be informative.

Acknowledgment *Conflicts of Interest*: None.

References

1. Moser M. Historical perspectives on the management of hypertension. J Clin Hypertens. 2006;8(8 Suppl 2):15–20; quiz 39.
2. Allen EV. Sympathectomy for essential hypertension. Circulation. 1952;6(1):131–40.
3. Lobay D. Rauwolfia in the treatment of hypertension. Integr Med (Encinitas). 2015;14(3):40–6.
4. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The Seventh Report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA. 2003;289(19):2560–72.
5. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353(5):487–97.
6. Chapman RH, Benner JS, Petrilla AA, Tierce JC, Collins SR, Battleman DS, et al. Predictors of adherence with antihypertensive and lipid-lowering therapy. Arch Intern Med. 2005;165(10):1147–52.
7. World Health Organization. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization; 2003.
8. Chowdhury R, Khan H, Heydon E, Shroufi A, Fahimi S, Moore C, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. Eur Heart J. 2013;34(38):2940–8.
9. Caro JJ, Salas M, Speckman JL, Raggio G, Jackson JD. Persistence with treatment for hypertension in actual practice. CMAJ: Can Med Assoc J. 1999;160(1):31–7.
10. Steiner JF, Earnest MA. The language of medication-taking. Ann Intern Med. 2000;132(11):926–30.
11. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol. 2012;73(5):691–705.
12. Dharmarajan TS, Dharmarajan L. Tolerability of antihypertensive medications in older adults. Drugs Aging. 2015;32(10):773–96.
13. Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. Ann Intern Med. 2004;140(10):795–801.
14. Bardage C, Isacson DG. Self-reported side-effects of antihypertensive drugs: an epidemiological study on prevalence and impact on health-state utility. Blood Press. 2000;9(6):328–34.
15. Morgado M, Rolo S, Macedo AF, Pereira L, Castelo-Branco M. Predictors of uncontrolled hypertension and antihypertensive medication nonadherence. J Cardiovasc Dis Res. 2010;1(4):196–202.
16. Tedla YG, Bautista LE. Drug side effect symptoms and adherence to antihypertensive medication. Am J Hypertens. 2016;29(6):772–9.
17. Eaddy MT, Cook CL, O'Day K, Burch SP, Cantrell CR. How patient cost-sharing trends affect adherence and outcomes: a literature review. P T. 2012;37(1):45–55.
18. Steinman MA, Sands LP, Covinsky KE. Self-restriction of medications due to cost in seniors without prescription coverage. J Gen Intern Med. 2001;16(12):793–9.
19. Maciejewski ML, Farley JF, Parker J, Wansink D. Copayment reductions generate greater medication adherence in targeted patients. Health Aff. 2010;29(11):2002–8.
20. Iskedjian M, Einarson TR, MacKeigan LD, Shear N, Addis A, Mittmann N, et al. Relationship between daily dose frequency and adherence to antihypertensive pharmacotherapy: evidence from a meta-analysis. Clin Ther. 2002;24(2):302–16.
21. Kesselheim AS, Bykov K, Avorn J, Tong A, Doherty M, Choudhry NK. Burden of changes in pill appearance for patients receiving generic cardiovascular medications after myocardial infarction: cohort and nested case-control studies. Ann Intern Med. 2014;161(2):96–103.

22. Kesselheim AS, Misono AS, Shrank WH, Greene JA, Doherty M, Avorn J, et al. Variations in pill appearance of antiepileptic drugs and the risk of nonadherence. JAMA Intern Med. 2013;173(3):202–8.
23. Lumbreras B, Lopez-Pintor E. Impact of changes in pill appearance in the adherence to angiotensin receptor blockers and in the blood pressure levels: a retrospective cohort study. BMJ Open. 2017;7(3):e012586.
24. Marshall IJ, Wolfe CDA, McKevitt C. Lay perspectives on hypertension and drug adherence: systematic review of qualitative research. BMJ: Br Med J. 2012;345:e3953.
25. Kronish IM, Leventhal H, Horowitz CR. Understanding minority patients' beliefs about hypertension to reduce gaps in communication between patients and clinicians. J Clin Hypertens. 2012;14(1):38–44.
26. Shrank WH, Cox ER, Fischer MA, Mehta J, Choudhry NK. Patients' perceptions of generic medications: although most Americans appreciate the cost-saving value of generics, few are eager to use generics themselves. Health Aff (Project Hope). 2009;28(2):546–56.
27. Corrao G, Soranna D, La Vecchia C, Catapano A, Agabiti-Rosei E, Gensini G, et al. Medication persistence and the use of generic and brand-name blood pressure-lowering agents. J Hypertens. 2014;32(5):1146–53; discussion 53.
28. Ude M, Schuessel K, Quinzler R, Leuner K, Muller WE, Schulz M. Generic switch after ramipril patent expiry is not associated with decreased pharmacy refill compliance: a retrospective study using the DAPI database. J Hypertens. 2011;29(9):1837–45.
29. Bramley TJ, Gerbino PP, Nightengale BS, Frech-Tamas F. Relationship of blood pressure control to adherence with antihypertensive monotherapy in 13 managed care organizations. J Manag Care Pharm. 2006;12(3):239–45.
30. Ho PM, Magid DJ, Shetterly SM, Olson KL, Peterson PN, Masoudi FA, et al. Importance of therapy intensification and medication nonadherence for blood pressure control in patients with coronary disease. Arch Intern Med. 2008;168(3):271–6.
31. DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. Med Care. 2004;42(3):200–9.
32. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311(5):507–20.
33. Weber MA, Schiffrin EL, White WB, Mann S, Lindholm LH, Kenerson JG, et al. Clinical practice guidelines for the management of hypertension in the community. J Clin Hypertens. 2014;16(1):14–26.
34. Task Force for the management of arterial hypertension of the European Society of Hypertension, Task Force for the management of arterial hypertension of the European Society of Cardiology. 2013 ESH/ESC Guidelines for the management of arterial hypertension. Blood Press. 2013;22(4):193–278.
35. Duarte JD, Cooper-DeHoff RM. Mechanisms for blood pressure lowering and metabolic effects of thiazide and thiazide-like diuretics. Expert Rev Cardiovasc Ther. 2010;8(6):793–802.
36. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002;288(23):2981–97.
37. Osterberg LG, Urquhart J, Blaschke TF. Understanding forgiveness: minding and mining the gaps between pharmacokinetics and therapeutics. Clin Pharmacol Ther. 2010;88(4):457–9.
38. Alderman MH, Piller LB, Ford CE, Probstfield JL, Oparil S, Cushman WC, et al. Clinical significance of incident hypokalemia and hyperkalemia in treated hypertensive patients in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. Hypertension. 2012;59(5):926–33.
39. Dhalla IA, Gomes T, Yao Z, Nagge J, Persaud N, Hellings C, et al. Chlorthalidone versus hydrochlorothiazide for the treatment of hypertension in older adults: a population-based cohort study. Ann Intern Med. 2013;158(6):447–55.

40. Makam AN, Boscardin WJ, Miao Y, Steinman MA. Risk of thiazide-induced metabolic adverse events in older adults. J Am Geriatr Soc. 2014;62(6):1039–45.
41. Haria M, Wagstaff AJ. Amlodipine. A reappraisal of its pharmacological properties and therapeutic use in cardiovascular disease. Drugs. 1995;50(3):560–86.
42. Yusuf S. Clinical, public health, and research implications of the Heart Outcomes Prevention Evaluation (HOPE) Study. Eur Heart J. 2001;22(2):103–4.
43. Overlack A. ACE inhibitor-induced cough and bronchospasm. Drug Saf. 1996;15(1):72–8.
44. Kaufman MB. ACE inhibitor-related angioedema: are your patients at risk? Pharm Ther. 2013;38(3):170–2.
45. Baram M, Kommuri A, Sellers SA, Cohn JR. ACE inhibitor-induced angioedema. J Allergy Clin Immunol Pract. 2013;1(5):442–5.
46. Gregoire JP, Moisan J, Guibert R, Ciampi A, Milot A, Cote I, et al. Tolerability of antihypertensive drugs in a community-based setting. Clin Ther. 2001;23(5):715–26.
47. Carlberg B, Samuelsson O, Lindholm LH. Atenolol in hypertension: is it a wise choice? Lancet. 2004;364(9446):1684–9.
48. Ripley TL, Saseen JJ. β-blockers. Ann Pharmacother. 2014;48(6):723–33.
49. Van Bortel LM, Fici F, Mascagni F. Efficacy and tolerability of nebivolol compared with other antihypertensive drugs: a meta-analysis. Am J Cardiovasc Drugs. 2008;8(1):35–44.
50. Slim HB, Black HR, Thompson PD. Older blood pressure medications—do they still have a place? Am J Cardiol. 2011;108(2):308–16.
51. Powers BJ, Coeytaux RR, Dolor RJ, Hasselblad V, Patel UD, Yancy WS, et al. Updated report on comparative effectiveness of ACE inhibitors, ARBs, and direct renin inhibitors for patients with essential hypertension: much more data, little new information. J Gen Intern Med. 2012;27(6):716–29.
52. Fisher ND, Meagher EA. Renin inhibitors. J Clin Hypertens. 2011;13(9):662–6.
53. Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet. 2002;359(9311):995–1003.
54. Heart Outcomes Prevention Evaluation Study Investigators, Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. N Engl J Med. 2000;342(3):145–53.
55. Cardinal H, Monfared AA, Dorais M, LeLorier J. A comparison between persistence to therapy in ALLHAT and in everyday clinical practice: a generalizability issue. Can J Cardiol. 2004;20(4):417–21.
56. Kronish IM, Woodward M, Sergie Z, Ogedegbe G, Falzon L, Mann DM. Meta-analysis: impact of drug class on adherence to antihypertensives. Circulation. 2011;123(15):1611–21.
57. Ritchey M, Chang A, Powers C, Loustalot F, Schieb L, Ketcham M, et al. Vital signs: disparities in antihypertensive medication nonadherence among Medicare part D beneficiaries—United States, 2014. MMWR Morb Mortal Wkly Rep. 2016;65(36):967–76.
58. Tajeu GS, Kent ST, Kronish IM, Huang L, Krousel-Wood M, Bress AP, et al. Trends in antihypertensive medication discontinuation and low adherence among Medicare beneficiaries initiating treatment from 2007 to 2012. Hypertension. 2016;68(3):565–75.
59. Ah YM, Lee JY, Choi YJ, Kim B, Choi KH, Kong J, et al. Persistence with antihypertensive medications in uncomplicated treatment-naive patients: effects of initial therapeutic classes. J Korean Med Sci. 2015;30(12):1800–6.
60. Schulz M, Krueger K, Schuessel K, Friedland K, Laufs U, Mueller WE, et al. Medication adherence and persistence according to different antihypertensive drug classes: a retrospective cohort study of 255,500 patients. Int J Cardiol. 2016;220:668–76.
61. Qvarnstrom M, Kahan T, Kieler H, Brandt L, Hasselstrom J, Bostrom KB, et al. Persistence to antihypertensive drug classes: a cohort study using the Swedish primary care cardiovascular database (SPCCD). Medicine (Baltimore). 2016;95(40):e4908.
62. Choi YJ, Ah YM, Kong J, Choi KH, Kim B, Han N, et al. Implication of different initial beta blockers on treatment persistence: atenolol vs new-generation beta blocker, a population-based study. Cardiovasc Ther. 2016;34(4):268–75.

63. Moise N, Schwartz J, Bring R, Shimbo D, Kronish IM. Antihypertensive drug class and adherence: an electronic monitoring study. Am J Hypertens. 2015;28(6):717–21.
64. Dickerson JE, Hingorani AD, Ashby MJ, Palmer CR, Brown MJ. Optimisation of antihypertensive treatment by crossover rotation of four major classes. Lancet. 1999;353(9169):2008–13.
65. Deary AJ, Schumann AL, Murfet H, Haydock SF, Foo RS, Brown MJ. Double-blind, placebo-controlled crossover comparison of five classes of antihypertensive drugs. J Hypertens. 2002;20(4):771–7.
66. Edmonds D, Huss R, Jeck T, Mengden T, Schubert M, Vetter W. Individualizing antihypertensive therapy with enalapril versus atenolol: the Zurich experience. J Hypertens Suppl. 1990;8(4):S49–52.
67. Waeber B, Burnier M, Nussberger J, Brunner HR. Trials using a crossover design and ambulatory blood pressure recordings to determine the efficacy of antihypertensive agents in individual patients. J Hypertens Suppl. 1990;8(4):S37–41.
68. Sharma P, Fatibene J, Ferraro F, Jia H, Monteith S, Brown C, et al. A genome-wide search for susceptibility loci to human essential hypertension. Hypertension. 2000;35(6):1291–6.
69. Gong Y, McDonough CW, Wang Z, Hou W, Cooper-DeHoff RM, Langaee TY, et al. Hypertension susceptibility loci and blood pressure response to antihypertensives: results from the pharmacogenomic evaluation of antihypertensive responses study. Circ Cardiovasc Genet. 2012;5(6):686–91.
70. Brunner HR, Menard J, Waeber B, Burnier M, Biollaz J, Nussberger J, et al. Treating the individual hypertensive patient: considerations on dose, sequential monotherapy and drug combinations. J Hypertens. 1990;8(1):3–11; discussion 3–9.
71. Duan N, Kravitz RL, Schmid CH. Single-patient (n-of-1) trials: a pragmatic clinical decision methodology for patient-centered comparative effectiveness research. J Clin Epidemiol. 2013;66(8 Suppl):S21–8.
72. Kravitz RL, Duan N, editors, and the DEcIDE Methods Center N-of-1 Guidance Panel (Duan N, Eslick I, Gabler NB, Kaplan HC, Kravitz RL, Larson EB, Pace WD, Schmid CH, Sim I, Vohra S). Design and implementation of N-of-1 trials: a user's guide. Rockville; 2014.
73. Mahon J, Laupacis A, Donner A, Wood T. Randomised study of n of 1 trials versus standard practice. BMJ. 1996;312(7038):1069–74.
74. Shiffman S, Stone AA, Hufford MR. Ecological momentary assessment. Annu Rev Clin Psychol. 2008;4:1–32.
75. Faria C, Wenzel M, Lee KW, Coderre K, Nichols J, Belletti DA. A narrative review of clinical inertia: focus on hypertension. J Am Soc Hypertens. 2009;3(4):267–76.
76. Phillips LS, Twombly JG. It's time to overcome clinical inertia. Ann Intern Med. 2008;148(10):783–5.
77. Stone AA, Shiffman S, Schwartz JE, Broderick JE, Hufford MR. Patient compliance with paper and electronic diaries. Control Clin Trials. 2003;24(2):182–99.
78. Larson EB, Ellsworth AJ, Oas J. Randomized clinical trials in single patients during a 2-year period. JAMA. 1993;270(22):2708–12.
79. Gabler NB, Duan N, Vohra S, Kravitz RL. N-of-1 trials in the medical literature: a systematic review. Med Care. 2011;49(8):761–8.
80. Nikles CJ, Yelland M, Glasziou PP, Del Mar C. Do individualized medication effectiveness tests (n-of-1 trials) change clinical decisions about which drugs to use for osteoarthritis and chronic pain? Am J Ther. 2005;12(1):92–7.
81. Nikles CJ, Clavarino AM, Del Mar CB. Using n-of-1 trials as a clinical tool to improve prescribing. Br J Gen Pract. 2005;55(512):175–80.
82. Tarn DM, Heritage J, Paterniti DA, Hays RD, Kravitz RL, Wenger NS. Physician communication when prescribing new medications. Arch Intern Med. 2006;166(17):1855–62.
83. Harmon G, Lefante J, Krousel-Wood M. Overcoming barriers: the role of providers in improving patient adherence to antihypertensive medications. Curr Opin Cardiol. 2006;21(4):310–5.
84. Krumholz HM. Variations in health care, patient preferences, and high-quality decision making. JAMA. 2013;310(2):151–2.

85. Krumholz HM, Barreto-Filho JA, Jones PG, Li Y, Spertus JA. Decision-making preferences among patients with an acute myocardial infarction. JAMA Intern Med. 2013;173(13):1252–7.
86. Elley CR, Gupta AK, Webster R, Selak V, Jun M, Patel A, et al. The efficacy and tolerability of 'polypills': meta-analysis of randomised controlled trials. PLoS One. 2012;7(12):e52145.
87. Conn VS, Ruppar TM, Chase JA, Enriquez M, Cooper PS. Interventions to improve medication adherence in hypertensive patients: systematic review and meta-analysis. Curr Hypertens Rep. 2015;17(12):94.

Medication Persistence in Hypertension in General Practice

13

Miriam Qvarnström, Björn Wettermark, and Thomas Kahan

13.1 Hypertensive Patients in Primary Health Care

Most patients with hypertension are managed in primary health care [1–3]. In Sweden, around half of the patients with a diagnosis of essential hypertension receive this diagnosis in primary health care only [4, 5]. Studies on medication persistence to antihypertensive drug treatment in primary health care show disappointing results, with one third of the patients discontinuing their medication within 2 years after initiation of treatment [6, 7]. For most patients, hypertension goes with no symptoms. Many patients and health care providers consider hypertension a marker for increased risk of disease later in life and do not consider high blood pressure a disease. This constitutes a problem for both health care providers and patients when discussing antihypertensive treatment. Although both parts consider treatment something necessary in order to reduce health problems in the future, they foresee no immediate beneficial effects. Hence, they miss having focus on the problem of

M. Qvarnström, M.Sc. Pharm., Ph.D.
Division of Cardiovascular Medicine, Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden
e-mail: miriam.qvarnstrom@ki.se

B. Wettermark, M.Sc. Pharm., Ph.D.
Centre for Pharmacoepidemiology, Department of Medicine/Solna, Karolinska Institutet, Stockholm, Sweden

Public Healthcare Services Committee, Stockholm County Council, Stockholm, Sweden
e-mail: bjorn.wettermark@sll.se

T. Kahan, M.D., Ph.D. (✉)
Division of Cardiovascular Medicine, Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Stockholm, Sweden

Department of Cardiology, Danderyd University Hospital Corporation, Stockholm, Sweden
e-mail: thomas.kahan@sll.se

M. Burnier (ed.), *Drug Adherence in Hypertension and Cardiovascular Protection*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-76593-8_13

hypertension at present, where elevated blood pressure will promote target organ damage, with important and often irreversible later consequences. Studies on medication persistence are important, as they may be valuable tools in identifying patient groups in need of targeted interventions to improve early blood pressure control and to prevent cardiovascular complications.

13.2 Definition of Medication Persistence

During the past decades, research groups have tried to come up with the best definitions for medication adherence, compliance, and persistence. However, researcher in this field may still find reports mixing these terms and using them inconsequently. This posts the question as to why it is necessary to differentiate between medication adherence (or compliance) and persistence? The simple answer is that adherence (or compliance) and persistence measure different things. Adherence and compliance, now considered synonyms, measure how well the patient takes their medication, while medication persistence measure for how long the patient takes their medication [8] (Fig. 13.1). Both terms affect clinical outcome in different ways. Thus, it is crucial to separate them when analysing medication-taking behaviour, in order to fully understand the mechanisms. Furthermore, correct terminology is also important in order to distinguish adherence from persistence, which is crucial to allow for comparisons of results between studies of medication persistence rates [9].

Although many different definitions of adherence or compliance, and persistence have been proposed, for the purpose of this text we will focus on three recently published major reviews [8–10]. First, Caetano et al. [10] made a literature review of all published papers between 1997 and 2005 on medication persistence towards statins and antihypertensive treatment. They found inconsistencies in the definitions of persistence and the methods by which it was measured. They proposed that the standard operational definition of persistence should not only consider total

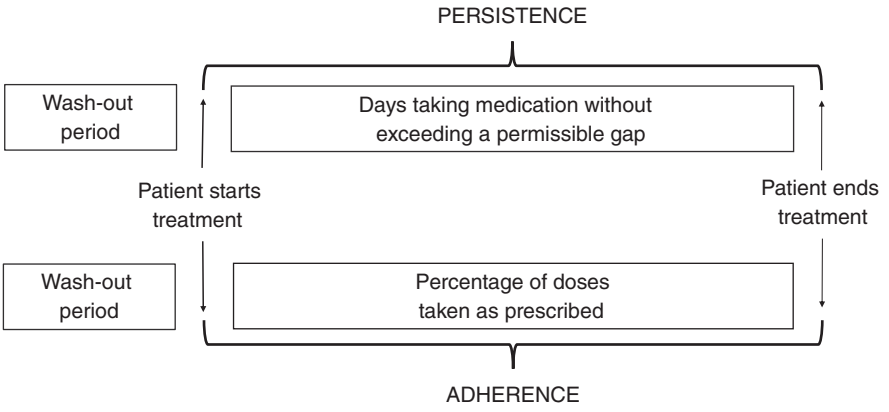


Fig. 13.1 Medication persistence defined as number of days on treatment without exceeding a permissible gap

duration of therapy, but also the intensity of medication-taking behaviour within this interval.

Second, in 2008 the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) Medication Compliance and Persistence Work Group, led by Joyce Cramer, published a review on the terminology and definitions used in studies observing medication adherence and persistence [8]. Their extensive investigations of all publications reporting on adherence, compliance, or persistence came up with two distinct definitions for compliance and persistence. They also concluded that the term compliance was synonymous with medication adherence. However, today the term adherence is much more commonly used, due to its different connotation. Compliance implies that the patient does what the physician says, while adherence relates more to the communication between patient and the physician. According to Cramer et al. [8], medication persistence may be defined as "the duration of time from initiation to discontinuation of therapy".

Finally, 4 years after Cramer et al. published their review [8], Vrijens et al. postulated a new and slightly different definition of medication adherence and persistence [9]. In contrast to the definition by Cramer et al., Vrijens et al. considered the term medication persistence to be a part of medication adherence, rather than seeing them as two unique terms. This is further illustrated in a subsequent publication [11], where the authors conclude that medication adherence is "the process by which patients take their medication as prescribed, further divided into three quantifiable phases: 'Initiation', 'Implementation' and 'Discontinuation'".

13.3 Therapy Versus Class Medication Persistence

Medication persistence can be divided into therapy persistence and class persistence. However, these terms are usually not specifically reported in the published literature, making it difficult for the reader to interpret the results. When therapy persistence is studied in the field of hypertension, we are interested in whether the patient is on any antihypertensive drug therapy. If class persistence is investigated, our interest is whether the patient is more persistent to the specific antihypertensive drug class the subject was initiated on. For example, if a patient is initiated on a beta blocker and switches to a calcium channel blocker, the patient is considered therapy persistent, but not class persistent. Given that the same method and study population is used, therapy persistence minus class persistence may be considered equal to the proportion of patients switching antihypertensive therapy.

13.4 How to Measure Medication Persistence

The persistence rate can be affected by the time frame and the method used in the study, but generally persistence rate decreases with time [12]. To study medication persistence, we need objective and longitudinal data. Therefore, registers on pharmacy claims data have been proposed as the golden standard in medication persistence research [11].

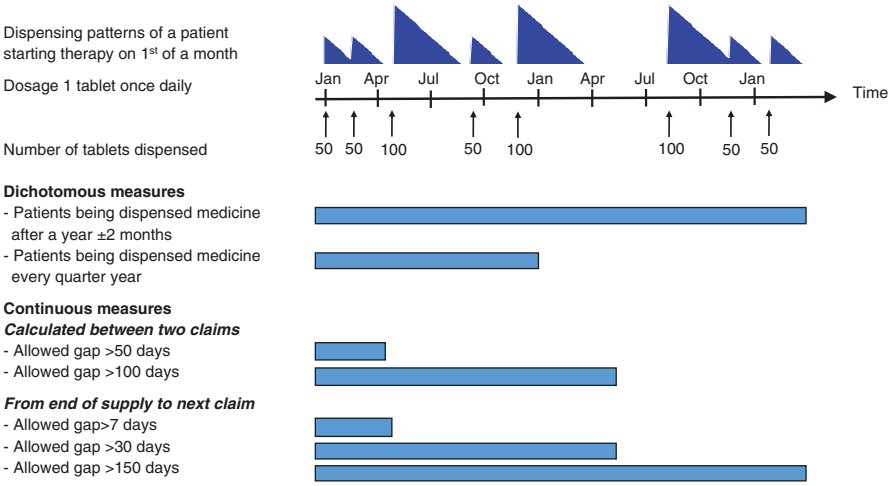


Fig. 13.2 An illustration of different methods for the calculation of medication persistence. This is exemplified for a hypothetical patient, showing her dispensing record during a 2-year period. Horizontal bars show how long time the patient will be classified as persistent. Developed and modified from a concept by [10]

There are different ways of calculating persistence, depending on the availability of structured information in the database (Fig. 13.2). The most simple methods are dichotomous, determining whether the patients have claimed a prescription or not after a certain time period. Such methods provide a somewhat crude picture. Hence, more sophisticated continuous analyses of each patient dispensing patterns are preferred. In order to conduct analyses of medication persistence, the researchers need first to consider the allowed gap, i.e. the number of days the patient can be without medication, but still be considered persistent to the antihypertensive therapy. This is well illustrated by several studies [8, 13]. The gap length is mostly influenced by the type of drug and by the regulations on filling prescriptions for different countries. Since antihypertensive medication can be considered chronic, will be taken every day, and mostly once daily when treating hypertension, relatively few aspects on gap length need to be considered when studying antihypertensive drug treatment.

Second, if the researcher is interested in patients newly initiated on antihypertensive treatment, they need to consider the wash-out period, i.e. for how long the patient needs to have been free of medical therapy to be considered newly initiated on treatment. Furthermore, the researcher must consider how to deal with patients in primary health care newly diagnosed with hypertension, where a large proportion will fill their first prescription, but some may not fill their second prescription. However, many of these patients will start antihypertensive treatment later, and this needs to be taken into account. The outstanding question is how to define a patient as “newly” initiated on treatment.

Third, it is important to consider the reimbursement system in the country of which the study is conducted. This can have major impact on how the patients are

filling their prescriptions. Most high income countries have limited patient copayment for drugs. This will increase the likelihood that patients fill their prescriptions, without actually taking them. However, if patients fill their prescriptions earlier than expected, considering the number of tablets prescribed, tablets are accumulated. A way to acknowledge this is through accumulating former prescriptions onto the latter filled prescription, when calculating persistence. Fourth, it is important to reflect on how medication persistence is to be measured, depending on types of data sources available. Using algorithms to extract dosage texts, in order to calculate the number of days the patient has taken the drug in relation to how much he or she should, is optimal. However, few databases contain structured information on prescribed doses. Thus, many researchers estimate medication persistence only from filled prescriptions with, e.g. 3 or 4 months of interval between filled prescriptions. The implications of different definitions of allowed gap are shown in Fig. 13.2.

13.5 Data Sources

There is a wide range of data sources that could be used to measure persistence to drug therapy. These may be either primary or secondary. Primary data sources refer to the original data collected directly by the investigator conducting the research for a particular purpose [14]. Secondary data sources encompass previously collected data, i.e. available data, which have not been generated for a specific research purpose but can be adapted to the analysis of a new research question. In studies of persistence, secondary data sources are preferred. These sources are not confounded by the patient being aware of the data collection with the purpose of monitoring persistence.

Secondary data sources available include electronic health records, pharmacy dispensing and claims databases, and various patient registries constructed to monitor quality of care in different disease conditions [15]. For persistence studies, registers on pharmacy claims data have been proposed as the golden standard [11]. The rationale behind this is the fact that these sources represent data closer to the actual drug consumption of the patients than medical records. Furthermore, such registers are often complete, enabling long time follow-up with large numbers of patients, and they may not be subject of any recall bias or desirability bias. An overview of the advantages and disadvantages with the different data sources are given in Table 13.1.

Some pharmacy claims databases provide the opportunity of record linkage between dispensed prescriptions and diagnoses. However, it is important to acknowledge that most pharmacy claims databases do not contain information on diagnoses. Consequently, many scientific studies assessed persistence to antihypertensive drugs regardless of indication they were prescribed for [16]. This may give misleading conclusions for hypertension, since a large proportion of patients receive antihypertensive for other conditions such as angina pectoris, atrial fibrillation, heart failure, or for secondary prevention after an acute coronary syndrome.

To increase our knowledge about medication persistence, pharmacy dispensing databases need to be complemented by other sources, such as information from

Table 13.1 Data sources available to measure medication persistence in the treatment of hypertension

Data source	Advantages	Disadvantages
Surveys to patients	May provide patient perspectives and factors explaining poor medication persistence	Affected by communication skills of interviewers and questions formulated, desirability bias, recall bias
Pharmacy claims databases	Inexpensive, large sample sizes (or complete populations), long time-series, data collected for other purposes than monitoring medication persistence, may be linked to diagnoses and sociodemographic information	Prescriptions may be missing, if obtained outside the system, sensitive to reimbursement and administrative rules, may not identify barriers for the detected non-persistence, may not identify discontinuation verbally advised by prescriber
Electronic health records	May provide clinical data (e.g. blood pressures, laboratory data) to assess persistence in relation to, may provide information on practice/physician characteristics influencing medication persistence	Sometimes problems with poor data quality and validity, patients may not redeem their prescriptions, may provide incomplete drug utilization histories for patients who receive care from other prescribers located in different health care settings

electronic health records containing blood pressures, laboratory data, and life style factors. However, it is important to acknowledge that prescription data documented in health records reflect the behaviour of the prescriber, rather than the patient, who may chose not to go to the pharmacy to claim the prescription [17]. Furthermore, since electronic health records are usually contained within a certain primary health care practice, they may provide incomplete drug utilization histories for patients who receive care also from other prescribers in different health care settings.

Patients are the end users of drugs, and their perspectives on persistence are therefore crucial. It is possible to study medication persistence through questionnaire to collect information that is impossible to include elsewhere. An example would be if we want to study attitudes of patients, or quality of life, in relation to medication persistence.

Recommendations for registry studies on medication persistence in hypertension are summarized in Table 13.2.

13.6 Ethics in Register Based Studies of Medication Persistence

The use of registries may raise concerns around privacy, confidentiality, and security of personal health data [15]. Privacy refers to the right of individuals to keep information about themselves from being disclosed to others and to be free from surveillance or interference from other individuals, organizations, or the government [18]. Confidentiality addresses issues of how personal data may be stored and used by the organization that collected the data and the extent to which the included individuals can give permission for uses [19]. Security can be defined as the procedural and technical measures required to prevent unauthorized access, modification, use, and

Table 13.2 Recommendations for registry studies on medication persistence in hypertension

1.	Use registries on pharmacy claims when available since these have been proposed as the gold standard data source for research on medication persistence
2.	Use databases with information on diagnoses and as much clinical information as possible (e.g. recorded diagnosis of hypertension, blood pressures, comorbidities, body mass index, and other cardiovascular risk factors)
3.	Apply record linkage, when feasible, using each patient's unique identifier to assess the clinical information in relation to data on prescription claims
4.	Describe your study population by age, sex, socio-economy, comorbidity, and care provider characteristics; and adjust or stratify for these factors in the analyses
5.	Apply an appropriate time windows in the data analyses; and take into account both an appropriate wash-out period to identify patients initiated on therapy, and days of gap to determine discontinuation
6.	Describe the reimbursement systems for medications of the country, as this can affect the pattern of how patients fill their prescriptions
7.	Adapt the method to the context of your country and setting. Consider other country-specific factors than the reimbursement system (e.g. health care organization and financing, guidelines or regulations), which can affect how the patient will fill their prescriptions
8.	Provide a good description of the persistence construct being measured, the measure being used (including any treatment reference time window) and any permissible gap period
9.	Perform sensitivity analyses by varying the wash-out period (to identify incident patients) and the gap length (to determine discontinuation)
10.	Combine register-based assessment with other methods (e.g. questionnaires, interviews, electronic drug box monitoring, or drug concentration measurements)

dissemination of data stored or processed in a computer system, to prevent any deliberate denial of service, and to protect the system in its entirety from physical harm [20].

Based on the Declarations of Helsinki from the World Medical Association, it is a basic right of the patient to be assured that all of her medical and personal data are confidential [21]. Researchers active in the field have recognized these ethical issues and adopted methods to ensure that the confidentiality of individually identifiable data is maintained [22]. Often, all data are encrypted, and some variables are aggregated in order to make it impossible to identify individual patients. In most countries, Ethical Committee approval is needed to conduct research on registers. The European Commission has recently proposed a stronger and more coherent data protection framework for the European Union, The EU General Data Protection Regulation (GDPR) [23]. Hopefully, this will not prevent the opportunities for conducting research using electronic health databases and prescription registers. A too strict application of privacy rules might hinder the further development of studies on persistence using secondary data.

13.7 Patient-Related Factors Associated with Medication Persistence to Antihypertensive Treatment

Patients with medication persistence to antihypertensive treatment may lack awareness of long-term consequences of hypertension, or may not anticipate the importance of controlling a high blood pressure (Table 13.3). This is observed particularly in patients newly diagnosed with hypertension and/or newly initiated on antihypertensive treatment, who present with a lower rate of medication persistence, as

Table 13.3 Patient, physician, and health care organization-related factors likely associated with medication persistence

Patient-related factors	Sex, age, comorbidity, initial systolic blood pressure, education, income, country of birth, attitudes on a diagnosis of hypertension and on medication, perceived involvement in decision making
Physician-related factors	Continuity, sex, number of visits to health care provider, clinical inertia
Healthcare organization-related factors	Blood pressure monitoring, surveillance, potential incentive systems, local guidelines

compared to patients who are prevalent users of antihypertensive treatment or have established hypertension [24–26].

Studies from many different countries have investigated patient characteristics potentially associated with poor medication persistence. These include clinical, demographic, and socioeconomic factors, which are easy to collect from, e.g. registers, electronic medical records, or questionnaires. Thus, the most studied patient-related factors associated with medication persistence include age and sex [6, 7, 16, 24, 25, 27–42], followed by comorbidity [6, 7, 28–30, 32–36, 38, 40–42]. Generally, medication persistence increases with increasing age and is higher in women than in men. The association of medication persistence and comorbidity varies between comorbidities. Thus, persistence appears higher in patients with diabetes, suggesting that medication persistence is higher in patients with comorbidities that need (or have) special attention from health care and regular visits to health care professionals, but persistence is lower in concomitant depressive disease, identifying a potential risk group for discontinuation of antihypertensive medication.

Other patient-related factors such as income, insurance type, and educational level are not often reported, and information on blood pressure before initiation of antihypertensive drug treatment, country of birth, number of visits to physicians or other care providers, and drugs prescribed is more uncommon [6, 7, 27, 30, 32, 36, 41, 42]. Although less investigated, it seems that higher income, native-born citizens, and a high number of visits to the physician are all related to increased medication persistence. Whether these various factors might be more important in some countries than others is currently not well understood.

The potential association of patient attitudes towards the diagnosis of hypertension and antihypertensive medication has been studied in relation to medication *adherence* [43]. However, most of these studies are small and lack statistical power. Studies on patient attitudes in relation to medication *persistence* do not seem to have been published.

13.8 Physician-Related Factors Associated with Medication Persistence to Antihypertensive Treatment

Physicians initiating antihypertensive treatment often individualize treatment for the specific patient. They know that hypertension should be treated but they also have to include global cardiovascular risk and concomitant disease and other

conditions into consideration. The health care provider may also do an assessment of the patients past medication-taking behaviour. Physician and health care provider-related factors studied in relation to medication persistence include continuity and the speciality of the prescriber, where a higher number of prescribers influence treatment adherence in a negative way [44] (Table 13.3). However, few studies from primary health care have been published, and such studies are needed.

Clinical inertia is a condition when physicians or other health care providers fail to initiate or intensify therapy when indicated [45]. This condition is particularly common in hypertension and with other conditions for which resolution of patient symptoms do not guide care. Thus, there is evidence to suggest that antihypertensive drugs treatment is not intensified (more drug classes added) in patients who do not meet target blood pressure [46, 47].

13.9 Healthcare Organization-Related Factors Associated with Medication Persistence to Antihypertensive Treatment

Also factors related to health care organization may influence medication persistence significantly. There may be a lack of follow-up and of blood pressure monitoring of patients with elevated blood pressures after initiating antihypertensive drug treatment. This may be due to poor access to health care providers, inconvenience of appointment scheduling, lack of incentives for follow-up, or other organization-related factors (Table 13.3).

It is also important to acknowledge the large differences between countries in the major characteristics of the organization of primary health care. There are differences in the ratio of primary care physicians to population, and in the extent to which patients relate to individual doctors. Furthermore, there are large differences in the mode of payment of primary care physicians, as well as to what extent primary care physicians have a gatekeeping function in the health system, resulting in large differences in the use of specialist services. Practice characteristics such as workload, length of consultation, ordering of tests and reappointments also vary with differences in payment and gatekeeping arrangements [48].

Conclusion

Medication persistence in the treatment of hypertension is associated with a reduction in cardiovascular outcome. Thus, studies on medication persistence are important. They may be valuable tools in identifying patient groups in need of targeted interventions to improve early blood pressure control and to prevent cardiovascular complications.

References

1. Østbye T, Yarnall KS, Krause KM, Pollak KI, Gradison M, Michener JL. Is there time for management of patients with chronic diseases in primary care? Ann Fam Med. 2005;3(3):209–14.
2. Harris MF, Zwar NA. Care of patients with chronic disease: the challenge for general practice. Med J Aust. 2007;187(2):104–7.
3. Katz A, Martens P, Chateau D, Bogdanovic B, Koseva I. Do primary care physicians coordinate ambulatory care for chronic disease patients in Canada? BMC Fam Pract. 2014;15:148.
4. Carlsson AC, Wändell P, Ösby U, Zarrinkoub R, Wettermark B, Ljunggren G. High prevalence of diagnosis of diabetes, depression, anxiety, hypertension, asthma and COPD in the total population of Stockholm, Sweden—a challenge for public health. BMC Public Health. 2013;13:670.
5. Wallentin F, Wettermark B, Kahan T. Current antihypertensive drug therapy in Sweden in relation to gender, age, and comorbidity. J Clin Hypertens. 2018;20(1):106–14.
6. Friedman O, McAlister FA, Yun L, Campbell NR, Tu K. Antihypertensive drug persistence and compliance among newly treated elderly hypertensives in Ontario. Am J Med. 2010;123(2):173–81.
7. Qvarnström M, Kahan T, Kieler H, et al. Persistence to antihypertensive drug treatment in Swedish primary healthcare. Eur J Clin Pharmacol. 2013;69(11):1955–64.
8. Cramer JA, Roy A, Burrell A, et al. Medication compliance and persistence: terminology and definitions. Value Health. 2008;11(1):44–7.
9. Vrijens B, De Geest S, Hughes DA, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol. 2012;73(5):691–705.
10. Caetano PA, Lam JM, Morgan SG. Toward a standard definition and measurement of persistence with drug therapy: examples from research on statin and antihypertensive utilization. Clin Ther. 2006;28(9):1411–24.
11. Vrijens B, Heidbuchel H. Non-vitamin K antagonist oral anticoagulants: considerations on once- vs. twice-daily regimens and their potential impact on medication adherence. Europace. 2015;17(4):514–23.
12. Cramer JA, Benedict A, Muszbek N, Keskinaslan A, Khan ZM. The significance of compliance and persistence in the treatment of diabetes, hypertension and dyslipidaemia: a review. Int J Clin Pract. 2008;62(1):76–87.
13. Van Wijk BL, Klungel OH, Heerdink ER, de Boer A. Refill persistence with chronic medication assessed from a pharmacy database was influenced by method of calculation. J Clin Epidemiol. 2006;59:11–7.
14. Kothari C, Garg G. Research methodology: methods and techniques. 3rd ed. New Delhi: New Age International Publishers; 2014.
15. Eriksson I, Ibanez L. Secondary data sources for drug utilization research. In: Elseviers M, Wettermark B, Almadóttir AB, et al., editors. Drug utilization research—methods and applications. Wiley: Chichester; 2016.
16. Simons LA, Ortiz M, Calcino G. Persistence with antihypertensive medication: Australia-wide experience, 2004-2006. Med J Aust. 2008;188(4):224–7.
17. Cooke CE, Xing S, Lee HY, Belletti DA. You wrote the prescription, but will it get filled? J Fam Pract. 2011;60(6):321–7.
18. Rognehaugh R. The health information technology dictionary. Gaithersburg: Aspen Publishers; 1999.
19. The National Academies Collection: Reports funded by National Institutes of Health. In: Nass SJ, Levit LA, Gostin LO, editors. Beyond the HIPAA privacy rule: enhancing privacy, improving health through research. Washington, DC: National Academies Press (US); 2009.
20. Turn R, Ware WH. Privacy and security issues in information systems. Santa Monica: The RAND Corporation; 1976.

21. Beauchamp TL, Childres JF. Principles of biomedical ethics. 3rd ed. New York: Oxford University Press; 1989.
22. Merz JF, editor. A survey of international ethics practices in pharmacoepidemiology and drug safety. Pharmacoepidemiol Drug Saf. 2001;10:577–708.
23. Olsen J. Data protection and epidemiological research: a new EU regulation is in the pipeline. Int J Epidemiol. 2014;43(5):1353–4.
24. Caro JJ, Salas M, Speckman JL, Raggio G, Jackson JD. Persistence with treatment for hypertension in actual practice. CMAJ. 1999;160(1):31–7.
25. Bourgault C, Senecal M, Brisson M, Marentette MA, Gregoire JP. Persistence and discontinuation patterns of antihypertensive therapy among newly treated patients: a population-based study. J Hum Hypertens. 2005;19(8):607–13.
26. Perreault S, Lamarre D, Blais L, et al. Persistence with treatment in newly treated middle-aged patients with essential hypertension. Ann Pharmacother. 2005;39(9):1401–8.
27. Burke TA, Sturkenboom MC, Lu SE, Wentworth CE, Lin Y, Rhoads GG. Discontinuation of antihypertensive drugs among newly diagnosed hypertensive patients in UK general practice. J Hypertens. 2006;24(6):1193–200.
28. Elliott WJ, Plauschinat CA, Skrepnek GH, Gause D. Persistence, adherence, and risk of discontinuation associated with commonly prescribed antihypertensive drug monotherapies. J Am Board Fam Med. 2007;20(1):72–80.
29. Hasford J, Schröder-Bernhardi D, Rottenkolber M, Kostev K, Dietlein G. Persistence with antihypertensive treatments: results of a 3-year follow-up cohort study. Eur J Clin Pharmacol. 2007;63(11):1055–61.
30. Patel BV, Remigio-Baker RA, Mehta D, Thiebaud P, Frech-Tamas F, Preblick R. Effects of initial antihypertensive drug class on patient persistence and compliance in a usual-care setting in the United States. J Clin Hypertens (Greenwich). 2007;9(9):692–700.
31. Corrao G, Zambon A, Parodi A, et al. Discontinuation of and changes in drug therapy for hypertension among newly-treated patients: a population-based study in Italy. J Hypertens. 2008;26(4):819–24.
32. Vinker S, Alkalay A, Hoffman RD, Elhayany A, Kaiserman I, Kitai E. Long-term adherence to antihypertensive therapy: a survey in four primary care clinics. Expert Opin Pharmacother. 2008;9(8):1271–7.
33. Saleh SS, Szebenyi S, Carter JA, Zacher C, Belletti D. Patterns and associated health services costs of antihypertensive drug modifications. J Clin Hypertens (Greenwich). 2008;10(1):43–50.
34. Wong MC, Jiang JY, Gibbs T, Griffiths SM. Factors associated with antihypertensive drug discontinuation among Chinese patients: a cohort study. Am J Hypertens. 2009;22(7):802–10.
35. Nicotra F, Wettermark B, Sturkenboom MC, et al. Management of antihypertensive drugs in three European countries. J Hypertens. 2009;27(9):1917–22.
36. Tamblyn R, Abrahamowicz M, Dauphinee D, et al. Influence of physicians' management and communication ability on patients' persistence with antihypertensive medication. Arch Intern Med. 2010;170(12):1064–72.
37. Trimarco V, de Simone G, Izzo R, et al. Persistence and adherence to antihypertensive treatment in relation to initial prescription: diuretics versus other classes of antihypertensive drugs. J Hypertens. 2012;30(6):1225–32.
38. Ishisaka DY, Jukes T, Romanelli RJ, Wong KS, Schiro TA. Disparities in adherence to and persistence with antihypertensive regimens: an exploratory analysis from a community-based provider network. J Am Soc Hypertens. 2012;6(3):201–9.
39. Selmer R, Blix HS, Landmark K, Reikvam A. Choice of initial antihypertensive drugs and persistence of drug use—a 4-year follow-up of 78,453 incident users. Eur J Clin Pharmacol. 2012;68(10):1435–42.
40. Mancia G, Zambon A, Soranna D, Merlino L, Corrao G. Factors involved in the discontinuation of antihypertensive drug therapy: an analysis from real life data. J Hypertens. 2014;32(8):1708–15.

41. Ah YM, Lee JY, Choi YJ, et al. Persistence with antihypertensive medications in uncomplicated treatment-naive patients: effects of initial therapeutic classes. J Korean Med Sci. 2015;30(12):1800–6.
42. Qvarnström M, Kahan T, Kieler H, et al. Persistence to antihypertensive drug classes: a cohort study using the Swedish Primary Care Cardiovascular Database (SPCCD). Medicine (Baltimore). 2016;95(40):e4908.
43. Ross S, Walker A, MacLeod MJ. Patient compliance in hypertension: role of illness perceptions and treatment beliefs. J Hum Hypertens. 2004;18(9):607–13.
44. Hansen RA, Voils CI, Farley JF, et al. Prescriber continuity and medication adherence for complex patients. Ann Pharmacother. 2015;49(3):293–302.
45. Phillips LS, Branch WT, Cook CB, et al. Clinical inertia. Ann Intern Med. 2001;135(9):825–34.
46. Nieburg I, Kahan T. How to improve risk factor evaluation of hypertensive patients in primary care. Blood Press. 2010;19:176–81.
47. Holmquist C, Hasselström J, Hjerpe P, et al. Improved treatment and control of hypertension in Swedish primary care: results from the Swedish Primary Care Cardiovascular Database (SPCCD). J Hypertens. 2017;35:2102–8.
48. Gervas J, Perez Fernandez M, Starfield BH. Primary care, financing and gatekeeping in western Europe. Fam Pract. 1994;11:307–17.

Drug Adherence in Resistant Hypertension

14

Idir Hamdidouche, Vincent Jullien, Stéphane Laurent, and Michel Azizi

14.1 Introduction

According to the European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines [1], hypertension is defined as resistant to treatment when a therapeutic strategy that includes appropriate lifestyle measures plus a diuretic and two other antihypertensive drugs belonging to different classes at adequate doses (but not necessarily including a mineralocorticoid receptor antagonist) fails to lower office systolic blood pressure (SBP) and diastolic blood pressure (DBP) values to below 140 mmHg and 90 mmHg, respectively. The NICE-UK guidelines recommend that the three-drug regimen should preferentially include a renin angiotensin system (RAS) blocker (i.e., an angiotensin-converting enzyme inhibitor, ACEI, or angiotensin II receptor blocker, ARB, but not both), a

I. Hamdidouche · S. Laurent
Department of Pharmacology and Hypertension Unit, Hopital Europeen Georges Pompidou, Assistance-Publique Hopitaux de Paris, Paris, France

Paris-Descartes University, Paris, France

INSERM UMRS970, Paris, France

V. Jullien
Department of Pharmacology and Hypertension Unit, Hopital Europeen Georges Pompidou, Assistance-Publique Hopitaux de Paris, Paris, France

Paris-Descartes University, Paris, France

M. Azizi (✉)
Department of Pharmacology and Hypertension Unit, Hopital Europeen Georges Pompidou, Assistance-Publique Hopitaux de Paris, Paris, France

Paris-Descartes University, Paris, France

INSERM CIC1418, Paris, France
e-mail: michel.azizi@aphp.fr

M. Burnier (ed.), *Drug Adherence in Hypertension and Cardiovascular Protection*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-76593-8_14

long-acting calcium channel blocker (CCB) and a thiazide (or thiazide-like) diuretic in the absence of renal insufficiency [2]. The triple combination should be ideally given as a single-pill fixed-dose combination to improve adherence to treatment.

Despite the availability of multiple antihypertensive drugs, the prevalence of apparent resistant hypertension ranges from 5 to 30% of the overall hypertensive population [3, 4]. However, the prevalence of true resistant hypertension is lower (approximately 10%) after excluding pseudo-resistant hypertension. Pseudo-resistant hypertension may be due to (1) an alarm reaction during BP measurement called the white coat phenomenon, thus out-of-office BP measurements (ABPM or self-BP measurement at home) should be used, (2) a poor method of office BP measurement, (3) heavily calcified arteries in the elderly patients, and finally (4) suboptimal drug adherence [5–7].

Resistant hypertension is associated with a poor prognosis as shown by its association with target organ damage [8] and a high risk of occurrence of cardiovascular and renal events within a short time frame [5, 9].

True resistant hypertension is often multifactorial and may be favored by: (1) lifestyle factors such as obesity, excessive alcohol consumption, and high sodium intake; (2) intake of interfering drugs or substance; (3) undetected secondary forms of hypertension; (4) chronic kidney disease or arterial stiffening; and (5) obstructive sleep apnea [5–7].

Patients should be screened for a secondary cause of hypertension especially primary aldosteronism, atherosclerotic renal artery stenosis particularly in elderly patients or patients with chronic kidney disease [5–7]. Poor adherence to treatment should be identified but may be challenging in clinical practice (see below). Clinical inertia and the non-prescription of a rational triple therapy at adequate doses is another major factor contributing to inadequate BP control [10, 11].

Treatment combines lifestyle changes (reducing sodium intake), the discontinuation of interfering substances, and the sequential addition of antihypertensive drugs to the initial triple therapy. Indeed, the cornerstone of therapy is diuretic treatment to decrease volume overload, together with salt intake restriction, particularly in patients with chronic kidney disease. The fourth-line treatment should be a mineralocorticoid receptor (MR) antagonists (spironolactone 25–50 mg/day) as shown in the PATHWAY-2 study [12] and other randomized trials and their meta-analysis [13]. If BP still remains uncontrolled, the stepwise addition of a beta-blocker, an alpha-1-blocker, and a centrally acting alpha-agonist may be needed [5–7]. BP measurement should be performed regularly during follow-up to quantify the effects of the treatment modifications with careful monitoring of renal function, serum electrolyte levels, and fluid status.

14.2 Non-adherence in Resistant Hypertension

Medication adherence can be defined as the process by which patients take their medications as prescribed and can fluctuate with time for various reasons [14, 15]. Non-adherence to antihypertensive medications and lifestyle measures is a key

factor underlying resistance to treatment, and this remains a major public health challenge [16]. According to Vrijens, "non-adherence occurs when a patient does not initiate a new prescription, implement as prescribed, or persist with treatment" [14, 15]. In patients with long standing and apparent resistant hypertension and frequent associated comorbidities, non-adherence is probably due more to a defect in implementation and persistence than in initiation of treatment.

Drug non-adherence should be suspected in all clinical situations where the prescribed treatment is not associated with the expected clinical benefit. This is typically the case in apparent resistant hypertension as shown by several converging clinical facts. First, the determinants of drug non-adherence in hypertension overlap, at least partly, with the clinical characteristics of resistant hypertensive patients (young age, obese patients, with a high prevalence of depression and associated comorbidities and often treated with complex drug regimen); these characteristics make them vulnerable to the incorrect use of antihypertensive medications. Second, the adherence check by electronic pillbox monitoring or toxicological analyses improves the BP control in this subpopulation [17, 18], which further reinforces the partial responsibility of drug non-adherence in resistance to treatment. Third, various studies have reported an alarming rate of non-adherence in patients with apparent resistant hypertension by using direct measurement of antihypertensive drugs in urine or plasma by high-performance liquid chromatography coupled with mass spectrometry (HPLC-MS/MS), [19–23]. Thus, drug non-adherence is thus a real concern for clinicians when it comes to establishing the diagnosis of true resistant hypertension.

The prevalence of non-adherence to antihypertensive treatment is very high in apparent resistant hypertension. However, its precise estimates remain difficult to measure due to lack of robust definitions and gold-standard diagnostic methods, as evidenced by the large prevalence range (7–86%) reported in both observational studies and clinical trials [24]. Several observational studies from different countries showed that drug non-adherence as assessed by HPLC-MS/MS is much more common than initially reported, with more than 50% of patients with apparent resistant hypertension being completely or partially non-adherent to the prescribed treatment [19–23]. Despite the high prevalence of drug non-adherence in observational studies, drug adherence is seldom measured in clinical trials settings particularly in patients with resistant hypertension [25]. When measured, non-adherence was indeed very common even in the very controlled setting of a randomized controlled trial [26, 27]. We used ultra-high performance LC-MS/MS to assess drug adherence in the Renal Denervation for Hypertension (DENERHTN) randomized controlled in which renal denervation added to a standardized and optimized antihypertensive treatment was compared to the same standardized and optimized antihypertensive treatment alone in patients with ambulatory confirmed resistant hypertension. Despite patients were tightly monitored by providing monthly visits with the same dedicated healthcare team, signed a consent form for drug assay and no cost to the patient, the rate of non-adherence was still very high [27]. Almost ≈52% of patients were non-adherent to the prescribed antihypertensive therapy, with 13% of them taking none of the seven prescribed antihypertensive drugs after 6 months of

follow-up. Thus, beyond the clinical challenge of convincing patients with apparent resistant hypertension to adhere to their antihypertensive medication for both BP control and prognosis improvement, drug adherence may have also major, unpredictable effects on the results of clinical trials including patients with resistant hypertension [26, 28]. Measurement of adherence should thus be incorporated in drug and device development studies [15, 29].

14.3 Assessment and Monitoring of Adherence in Resistant Hypertension

An ideal method for assessing and monitoring drug adherence should be reliable, practical, simple, and relatively cost-effective. However, there is no method that meets all these criteria. Various direct and indirect methods for assessing adherence to drug treatments have been developed in the past years [16, 30]. The direct methods include the direct observation of treatment intake in a medicalized setting, such as a BP clinic, the detection of a drug or its metabolite in blood or urine, or the determination of a pharmacodynamic marker [16, 30]. Indirect methods include patient questionnaires [31], self-reports, patient diaries, pill counts, prescription refill rates, the assessment of patient clinical response, electronic drug monitoring systems, and the determination of physiological markers [16, 30]. Pharmacodynamic markers of exposure to a given antihypertensive treatment include, for example, bradycardia in patients on beta-blockers, hyperuricemia or gout in patients on diuretics, increases in plasma renin concentration in patients on diuretics or RAS blockers, increases in urine *N*-acetyl-seryl-aspartyl-lysyl-proline (AcSDKP) concentration in patients on ACEI [32] and drug-related side effects.

The selection of the method to assess drug adherence is conditioned by its availability in the clinical setting and also by study goals [24]. In clinical practice, adherence should be assessed systematically during every clinic visit for all patients with apparent resistant hypertension [33]. All medications and prescriptions should be reviewed with each patient at each clinical appointment. Patients may be asked how do they cope with their antihypertensive medications and associated co-prescriptions during their daily life by using validated questionnaires [31]. Although such patient self-report measures of adherence are known to be less accurate compared with direct measures by drug detection and can be manipulated by the patient [34], their use in a busy, resource limited clinical setting may have an educative value and may reinforce the relationship between patients and their care provider. So far, therapeutic drug monitoring based on LC-MS/MS to detect the presence of a given prescribed drug in plasma or urine samples is one of the best options to differentiate non-adherence from non-responsiveness among patients with apparently uncontrolled or resistant hypertension in clinical practice and in clinical trials [27, 28]. This approach is cost-effective [35] and can provide reliable information for the physician about his/her actual patient's adherence based on directly measured parameter. However, the non-detection of a drug is not sufficient to conclude with certainty that the patient is not complying with antihypertensive treatment. Indeed,

multiple factors may strongly influence the pharmacokinetics of antihypertensive drugs, resulting in their non-detection in biological samples [24, 33]. Conversely, the detection of significant quantities of drugs in plasma or urine is not sufficient to confirm optimal adherence to treatment on a daily basis. Indeed, patients often display better adherence to treatment during the week before and the week immediately after medical visits [30]. This phenomenon, known as "the toothbrush effect," may be amplified if the patients are aware that regular drug monitoring is carried out at each visit [30]. Therefore, these measurements give only an instant picture of adherence which is a dynamic process and can fluctuate over time. Electronic monitoring devices may also be of valuable help. However, such device may also introduce some behavioral biases, for example, increased adherence, and, as such, their results may not be applicable to the general practice.

In conclusion, each method for measuring treatment adherence has advantages and disadvantages, and the method chosen depends on availability in the clinical setting [30]. Some methods are easy to use (standardized questionnaire, determination of physiological variables), whereas others, such as drug detection or the direct observation of treatment intake, are much more difficult to implement. Finally, a combination of methods is likely the most effective approach because it can identify different components of non-adherence and is therefore recommended [16].

14.4 Non-adherence and Clinical Outcomes

During the past decades, non-adherence to treatment has been increasingly recognized as one major contributor of non-control of BP [21, 30, 36, 37] and poor cardiovascular prognosis [38]. Moreover, in patients with resistant hypertension, Beaussier et al. [28] showed that adherence to treatment not only contributes to optimal control of BP on the short term, but also to the regression of target organ damage, including changes in pulse wave velocity and left ventricular mass independently of BP changes. Overall, observational studies consistently showed that adherence to antihypertensive therapy is associated with better cardiovascular and renal prognosis [39–42]. The beneficial impact of adherence to treatment is also reported in patients with other cardiovascular diseases and even, in different type of diseases [43]. High adherence to any cardiovascular treatment was associated with 29% risk reduction in all-cause mortality in a recent meta-analysis including 44 individual studies, involving nearly two million participants [44]. Conversely, drug non-adherence is associated with a high risk of cardiovascular events in a short time frame in the general hypertensive population [38, 45], but less is known in patients with in apparent resistant hypertension [24]. Therefore, non-adherence to treatment undermines the benefits of evidence-based therapy, possibly contributing to thousands of deaths or major cardiovascular events, consequently inducing a major economic burden on the health system [15]. Finally, in clinical trials assessing new therapeutic strategies or new treatments in hypertension, non-adherence to treatment may lead to an underestimation of both the BP lowering efficacy and the adverse event rate [28].

14.5 Understanding and Predicting Non-adherence in Resistant Hypertension

The reasons for poor adherence to treatment are multifactorial [16]. Treatment-, patient-, physician-, and healthcare system-related factors promote drug non-adherence in patients with resistant hypertension but prediction of non-adherence remains challenging [24]. Understanding and accurately capturing factors associated with non-adherence may help targeting the subgroup of patients with poor adherence to avoid unnecessary and potentially harmful treatment intensification, decrease the number of medical visits at specialized clinics, and allow implementation of strategies to improve drug adherence.

14.5.1 Treatment-Related Factors

Therapeutic regimen complexity contributes largely to non-adherence in patients with resistant hypertension treated by multiple therapies especially in the presence of comorbid conditions (diabetes, dyslipidemia, coronary heart disease, chronic kidney disease, depression, etc.). Indeed, significant decreases in drug adherence were reported 1 year after treatment intensification in previously adherent patients with apparent resistant hypertension [46], suggesting that adherence declined with regimen complexity. Daily dosing frequency is also inversely related to adherence [47]. Patients' adherence may also be influenced by the antihypertensive drug class(es) used as shown by higher adherence to ARBs and ACEI and lower adherence to diuretics and beta-blockers in a meta-analysis including a general population of patients with hypertension [48]. However, the results of this meta-analysis may not be generalized to patients with apparent resistant hypertension, who are treated with multiple antihypertensive therapies. Indeed, several observational studies in patients with apparent resistant hypertension reported comparable and evenly distributed drug adherence to beta-blockers, diuretics, ARBs, or ACEI [20, 49]. Finally, drug-related side effect may influence negatively drug adherence by altering quality of life especially in previously asymptomatic patients (e.g., coughing with ACEI, flushing or leg edemas with CCBs, sexual dysfunction with diuretics, spironolactone or beta-blockers, gout with diuretics, symptomatic hypotension, etc.).

14.5.2 Patients-, Physician-, and Healthcare System-Related Factors

Sociodemographic factors, such as age, ethnicity, sex, income, educational level, and cognitive function, may impact adherence to antihypertensive therapy [19, 49, 50]. Indeed, young [19, 49] and female patients were more likely to exhibit non-adherence than men in apparent resistant hypertension [34, 50]. Non-white ethnicity and history of chronic heart disease are also related to non-adherence [50].

Psychosocial factors, depression, excessive alcohol consumption, poor adherence with lifestyle changes, lack of health insurance, unemployment, low income, and the reward feeling of being recognized as a diseased person by the familial or the professional environment with associated financial and/or societal benefits, have also been associated with poor adherence with drug treatment [51–53]. It is also important to take into account the patient's viewpoint and beliefs about the causes and effects of hypertension and its treatment which is far away from the physician's perception [54]. Other factors include practical barriers to treatment and poor access to busy non-empathetic physicians, a poor healthcare provider–patient relationship, high drug, and appointment costs [51–53]. Too little time spent with patients; lack of explanation about hypertension, BP goals, the treatment strategy, the balance between the benefits and risk of treatment, and the need for life-long treatment; or lack of consideration of the patient's complaints about drug-related side effects by the physician contribute all to a poor healthcare provider–patient relationship [55]. Indeed, in a chronic asymptomatic disease such as hypertension, the absence of perceived and immediate benefits from antihypertensive medications, which is often associated with the possibility of immediate drug-induced side effects, may discourage drug intake by the patients. Thus, perception of risks and benefits of medications impact greatly non-adherence in resistant hypertension.

Finally, although some of the aforementioned factors may predominantly contribute to non-adherence in each individual patient, none of them taken individually may completely explain the complexity of patient's behavior and attitude towards adherence to drug therapy. The combination of the contributing factors makes patients with apparent resistant hypertension even more vulnerable to the incorrect use of antihypertensive therapy. Overcoming and improving adherence to drug therapy and lifestyle measures is therefore mandatory to help maximizing the potential benefits of antihypertensive therapy.

14.6 Overcoming Non-adherence

Efforts should focus on improving measurement, predicting non-adherence and developing interventions to improve adherence in both daily practice settings and clinical trials.

To overcome poor adherence, a combined approach including improved and renewed patient–clinician dialogue, simplification of prescriptions by the use of fixed-dose combination [56], monitoring of prescription refills, and, if available, toxicological analyses or pill boxes is necessary. Such approach involves strong partnerships between patients, care providers, biologists running LC-MSMS platforms, pharmacologists, and payers [57]. Assessment of adherence during every outpatient visit may reinforce and renew care provider–patient relationships [24]. Open discussions on barriers to adherence, reinforcement of therapeutic education about the need for continued and life-long drug adherence, and addressing specific patient concerns may help for improving drug adherence [16]. In this context, implementation and enhancement of empowerment can promote self-management

skills that serve for the increase in drug adherence, as evidenced in other population with chronic disease [58]. Developing a routine for taking medication, use of electronic reminders and organizational tools are some of the simple educational strategies by which may improve drug adherence [16]. Moreover, the use of once-daily single-pill double or triple combination therapies reduces pill burden [59], simplifies treatment regimens without increasing the incidence of side effects, and may also improve adherence to treatment.

Multiple other interventions have also been shown to improve adherence in hypertension. Self-BP monitoring at home at best with teletransmission [60] may improve the patient's adherence with drug treatment, but clinical trials have reported mixed benefits [59]. In six of 11 randomized controlled trials included in a systematic review, the use of "multimodal complex" interventions involving self-BP measurement was associated with significant improvements in adherence to treatment

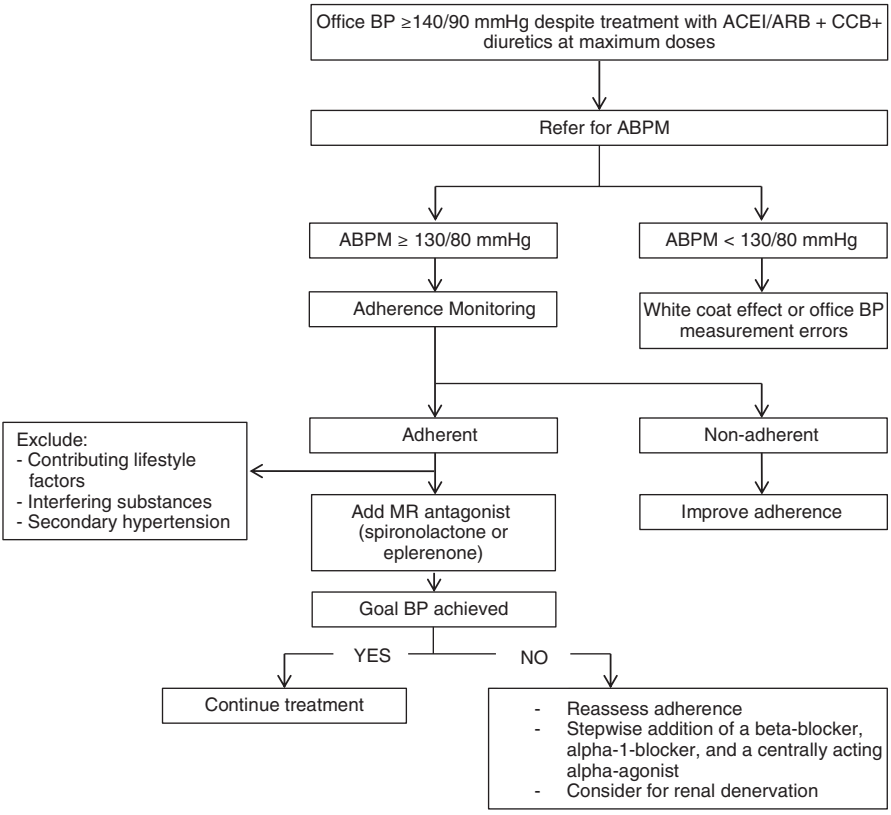


Fig. 14.1 Algorithm for the management of resistant hypertension. *CCB* indicates calcium channel blocker, *ARB* angiotensin receptor blocker, *ACEi* angiotensin-converting enzyme inhibitor, *MR* mineralocorticoid receptor, *ABPM* indicates ambulatory BP monitoring, *BP* blood pressure

[61]. Self-BP management with the self-titration of antihypertensive medication, using a precise treatment algorithm coupled to self-BP monitoring may improve adherence to treatment further, as shown in the TASMIN-SR randomized controlled trial [62]. However, these studies did not specifically include patients with resistant hypertension or monitor adherence with treatment, but it seems likely that the telemonitoring transmission of self-monitoring BP measurements and the self-titration of medication improve BP control through better adherence to treatment. These approaches require the active and motivated participation of well-educated and trained patients without cognitive deficiencies reducing their external applicability to all patients (Fig. 14.1).

Support from health professionals, including pharmacists and nurses, counseling, motivational support or cognitive behavioral therapy, and additional help from the family may also increase adherence to treatment [63]. Technological interventions for education, counseling, self-monitoring, feedback, and electronic reminders are increasingly being used, but the evidence concerning their efficacy for improving adherence to treatment is inconsistent [64].

Finally, the use of electronic pill monitors improves BP control, probably by improving adherence to treatment [65, 66], but these devices are expensive and not readily available outside of clinical trials. A new technology consisting of ingestible sensors embedded in tablets, a skin-worn receiver patch, and a mobile device based is in development to provide adherence patterns in real time by wirelessly observed therapy [67].

Conclusions

Non-adherence to antihypertensive therapy has become increasingly recognized as the dominant risk factor for apparent resistant hypertension. Undiagnosed or undeclared non-adherence may lead to (1) various additional (sometimes invasive and often expensive) diagnostic tests in specialized centers to identify the cause of the poor response to antihypertensive medications, (2) inappropriate intensification of antihypertensive treatments, and (3) excess use of healthcare system resources. Accurate, cost-effective and practical screening tools are needed to target interventions. Because drug non-adherence is recognized as a multifactorial phenomenon, interventions to improve it are likely a combination of different strategies. In a recent published systematic review of randomized controlled studies [63] to promote drug adherence in chronic medical conditions, the combination of educational, social, and behavioral strategies was effective at improving drug adherence but their implementation remains challenging when facing the increasing prevalence of hypertension and the resources usually available [68, 69]. The use of appropriate and personalized daily doses of the available drugs, efforts to decrease physician inertia, to improve compliance with treatment and access to healthcare, and to decrease treatment costs remain major objectives for reducing the incidence of resistant hypertension and the associated target organ damage and poor prognosis.

References

1. ESH/ESC Task Force for the Management of Arterial Hypertension. 2013 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC): ESH/ESC Task Force for the Management of Arterial Hypertension. J Hypertens. 2013;31(10):1925–38.
2. Krause T, Lovibond K, Caulfield M, McCormack T, Williams B, Guideline Development Group. Management of hypertension: summary of NICE guidance. BMJ. 2011;343:d4891.
3. Judd E, Calhoun DA. Apparent and true resistant hypertension: definition, prevalence and outcomes. J Hum Hypertens. 2014;28(8):463–8.
4. Achelrod D, Wenzel U, Frey S. Systematic review and meta-analysis of the prevalence of resistant hypertension in treated hypertensive populations. Am J Hypertens. 2015;28(3):355–61.
5. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD, et al. Resistant hypertension: diagnosis, evaluation, and treatment: a scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Circulation. 2008;117(25):e510–26.
6. Myat A, Redwood SR, Qureshi AC, Spertus JA, Williams B. Resistant hypertension. BMJ. 2012;345:e7473.
7. Vongpatanasin W. Resistant hypertension: a review of diagnosis and management. JAMA. 2014;311(21):2216–24.
8. Cuspidi C, Macca G, Sampieri L, Michev I, Salerno M, Fusi V, et al. High prevalence of cardiac and extracardiac target organ damage in refractory hypertension. J Hypertens. 2001;19(11):2063–70.
9. Egan BM, Zhao Y, Axon RN, Brzezinski WA, Ferdinand KC. Uncontrolled and apparent treatment resistant hypertension in the United States, 1988 to 2008. Circulation. 2011;124(9):1046–58.
10. Oliveria SA, Lapuerta P, McCarthy BD, L'Italien GJ, Berlowitz DR, Asch SM. Physician-related barriers to the effective management of uncontrolled hypertension. Arch Intern Med. 2002;162(4):413–20.
11. Sarafidis PA, Bakris GL. Resistant hypertension: an overview of evaluation and treatment. J Am Coll Cardiol. 2008;52(22):1749–57.
12. Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet. 2015;386(10008):2059–68.
13. Zhao D, Liu H, Dong P, Zhao J. A meta-analysis of add-on use of spironolactone in patients with resistant hypertension. Int J Cardiol. 2017;233:113–7.
14. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol. 2012;73(5):691–705.
15. Vrijens B, Antoniou S, Burnier M, de la Sierra A, Volpe M. Current situation of medication adherence in hypertension. Front Pharmacol. 2017;8:100.
16. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353(5):487–97.
17. Burnier M, Schneider MP, Chioléro A, Stubi CL, Brunner HR. Electronic compliance monitoring in resistant hypertension: the basis for rational therapeutic decisions. J Hypertens. 2001;19(2):335–41.
18. Brinker S, Pandey A, Ayers C, Price A, Raheja P, Arbique D, et al. Therapeutic drug monitoring facilitates blood pressure control in resistant hypertension. J Am Coll Cardiol. 2014;63(8):834–5.
19. Ceral J, Habrdova V, Vorisek V, Bima M, Pelouch R, Solar M. Difficult-to-control arterial hypertension or uncooperative patients? The assessment of serum antihypertensive drug levels to differentiate non-responsiveness from non-adherence to recommended therapy. Hypertens Res. 2011;34(1):87–90.

20. Jung O, Gechter JL, Wunder C, Paulke A, Bartel C, Geiger H, et al. Resistant hypertension? Assessment of adherence by toxicological urine analysis. J Hypertens. 2013;31(4):766–74.
21. Tomaszewski M, White C, Patel P, Masca N, Damani R, Hepworth J, et al. High rates of non-adherence to antihypertensive treatment revealed by high-performance liquid chromatography-tandem mass spectrometry (HP LC-MS/MS) urine analysis. Heart. 2014;100(11):855–61.
22. Hamdidouche I, Jullien V, Billaud EM, Boutouyrie P, Azizi M, Laurent S. Routine urinary detection of antihypertensive drugs for estimation of adherence to treatment: a cross sectional study. J Hypertens. 2015;33(Suppl 1):e93.
23. Patel P, Gupta PKC, White CMJ, Stanley AG, Williams B, Tomaszewski M. Screening for non-adherence to antihypertensive treatment as a part of the diagnostic pathway to renal denervation. J Hum Hypertens. 2016;30(6):368–73.
24. Hamdidouche I, Jullien V, Boutouyrie P, Billaud E, Azizi M, Laurent S. Drug adherence in hypertension: from methodological issues to cardiovascular outcomes. J Hypertens. 2017;35(6):1133–44.
25. Burnier M, Wuerzner G. Drug adherence monitoring in clinical trials: a necessity for a correct assessment of the efficacy and safety of antihypertensive therapies. J Hypertens. 2015;33(12):2395–8.
26. de Jager RL, de Beus E, Beeftink MMA, Sanders MF, Vonken E-J, Voskuil M, et al. Impact of medication adherence on the effect of renal denervation: the SYMPATHY trial. Hypertension. 2017;69(4):678–84.
27. Azizi M, Pereira H, Hamdidouche I, Gosse P, Monge M, Bobrie G, et al. Adherence to antihypertensive treatment and the blood pressure lowering effects of renal denervation in the renal denervation for hypertension (DENERHTN) trial. Circulation. 2016;134(12):847–57.
28. Beaussier H, Boutouyrie P, Bobrie G, Frank M, Laurent S, Coudoré F, et al. True antihypertensive efficacy of sequential nephron blockade in patients with resistant hypertension and confirmed medication adherence. J Hypertens. 2015;33(12):2526–33.
29. Mahfoud F, Böhm M, Azizi M, Pathak A, Durand Zaleski I, Ewen S, et al. Proceedings from the European clinical consensus conference for renal denervation: considerations on future clinical trial design. Eur Heart J. 2015;36(33):2219–27.
30. Burnier M, Wuerzner G, Struijker-Boudier H, Urquhart J. Measuring, analyzing, and managing drug adherence in resistant hypertension. Hypertension. 2013;62(2):218–25.
31. Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. J Clin Hypertens. 2008;10(5):348–54.
32. Azizi M, Ménard J, Peyrard S, Lièvre M, Marre M, Chatellier G. Assessment of patients' and physicians' compliance to an ACE inhibitor treatment based on urinary N-acetyl Ser-Asp-Lys-Pro determination in the Noninsulin-Dependent Diabetes, Hypertension, Microalbuminuria, Proteinuria, Cardiovascular Events, and Ramipril (DIABHYCAR) study. Diabetes Care. 2006;29(6):1331–6.
33. Berra E, Azizi M, Capron A, Høieggen A, Rabbia F, Kjeldsen SE, et al. Evaluation of adherence should become an integral part of assessment of patients with apparently treatment-resistant hypertension. Hypertension. 2016;68(2):297–306.
34. Pandey A, Raza F, Velasco A, Brinker S, Ayers C, Das SR, et al. Comparison of Morisky Medication Adherence Scale with therapeutic drug monitoring in apparent treatment-resistant hypertension. J Am Soc Hypertens. 2015;9(6):420–6.e2.
35. Kjeldsen SE, Os I. Cost-effectiveness of therapeutic drug monitoring in patients with resistant hypertension and improving patients' adherence. J Hypertens. 2014;32(12):2357–8.
36. Burnier M. Medication adherence and persistence as the cornerstone of effective antihypertensive therapy. Am J Hypertens. 2006;19(11):1190–6.
37. Bramley TJ, Gerbino PP, Nightengale BS, Frech-Tamas F. Relationship of blood pressure control to adherence with antihypertensive monotherapy in 13 managed care organizations. J Manag Care Pharm. 2006;12(3):239–45.
38. Mazzaglia G, Ambrosioni E, Alacqua M, Filippi A, Sessa E, Immordino V, et al. Adherence to antihypertensive medications and cardiovascular morbidity among newly diagnosed hypertensive patients. Circulation. 2009;120(16):1598–605.

39. Perreault S, Dragomir A, White M, Lalonde L, Blais L, Bérard A. Better adherence to antihypertensive agents and risk reduction of chronic heart failure. J Intern Med. 2009;266(2):207–18.
40. Perreault S, Dragomir A, Roy L, White M, Blais L, Lalonde L, et al. Adherence level of antihypertensive agents in coronary artery disease. Br J Clin Pharmacol. 2010;69(1):74–84.
41. Kettani F-Z, Dragomir A, Côté R, Roy L, Bérard A, Blais L, et al. Impact of a better adherence to antihypertensive agents on cerebrovascular disease for primary prevention. Stroke. 2009;40(1):213–20.
42. Roy L, White-Guay B, Dorais M, Dragomir A, Lessard M, Perreault S. Adherence to antihypertensive agents improves risk reduction of end-stage renal disease. Kidney Int. 2013;84(3):570–7.
43. Simpson SH, Eurich DT, Majumdar SR, Padwal RS, Tsuyuki RT, Varney J, et al. A meta-analysis of the association between adherence to drug therapy and mortality. BMJ. 2006;333(7557):15.
44. Chowdhury R, Khan H, Heydon E, Shroufi A, Fahimi S, Moore C, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. Eur Heart J. 2013;34(38):2940–8.
45. Corrao G, Parodi A, Nicotra F, Zambon A, Merlino L, Cesana G, et al. Better compliance to antihypertensive medications reduces cardiovascular risk. J Hypertens. 2011;29(3):610–8.
46. Daugherty SL, Powers JD, Magid DJ, Masoudi FA, Margolis KL, O'Connor PJ, et al. The association between medication adherence and treatment intensification with blood pressure control in resistant hypertension. Hypertension. 2012;60(2):303–9.
47. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther. 2001;23(8):1296–310.
48. Kronish IM, Woodward M, Sergie Z, Ogedegbe G, Falzon L, Mann DM. Meta-analysis: impact of drug class on adherence to antihypertensives. Circulation. 2011;123(15):1611–21.
49. Strauch B, Petrák O, Zelinka T, Rosa J, Somlóová Z, Indra T, et al. Precise assessment of noncompliance with the antihypertensive therapy in patients with resistant hypertension using toxicological serum analysis. J Hypertens. 2013;31(12):2455–61.
50. Irvin MR, Shimbo D, Mann DM, Reynolds K, Krousel-Wood M, Limdi NA, et al. Prevalence and correlates of low medication adherence in apparent treatment-resistant hypertension. J Clin Hypertens (Greenwich). 2012;14(10):694–700.
51. Mancia G, Zambon A, Soranna D, Merlino L, Corrao G. Factors involved in the discontinuation of antihypertensive drug therapy: an analysis from real life data. J Hypertens. 2014;32(8):1708–15.
52. Holt E, Joyce C, Dornelles A, Morisky D, Webber LS, Muntner P, et al. Sex differences in barriers to antihypertensive medication adherence: findings from the cohort study of medication adherence among older adults. J Am Geriatr Soc. 2013;61(4):558–64.
53. Cené CW, Dennison CR, Powell Hammond W, Levine D, Bone LR, Hill MN. Antihypertensive medication nonadherence in black men: direct and mediating effects of depressive symptoms, psychosocial stressors, and substance use. J Clin Hypertens. 2013;15(3):201–9.
54. Marshall IJ, Wolfe CDA, McKevitt C. Lay perspectives on hypertension and drug adherence: systematic review of qualitative research. BMJ. 2012;345:e3953.
55. Knight EL, Bohn RL, Wang PS, Glynn RJ, Mogun H, Avorn J. Predictors of uncontrolled hypertension in ambulatory patients. Hypertension. 2001;38(4):809–14.
56. Xie L, Frech-Tamas F, Marrett E, Baser O. A medication adherence and persistence comparison of hypertensive patients treated with single-, double- and triple-pill combination therapy. Curr Med Res Opin. 2014;30(12):2415–22.
57. Misono AS, Cutrona SL, Choudhry NK, Fischer MA, Stedman MR, Liberman JN, et al. Healthcare information technology interventions to improve cardiovascular and diabetes medication adherence. Am J Manag Care. 2010;16(12 Suppl HIT):SP82–92.
58. Hernandez-Tejada MA, Campbell JA, Walker RJ, Smalls BL, Davis KS, Egede LE. Diabetes empowerment, medication adherence and self-care behaviors in adults with type 2 diabetes. Diabetes Technol Ther. 2012;14(7):630–4.
59. Ogedegbe G, Schoenthaler A. A systematic review of the effects of home blood pressure monitoring on medication adherence. J Clin Hypertens (Greenwich). 2006;8(3):174–80.

60. Omboni S, Gazzola T, Carabelli G, Parati G. Clinical usefulness and cost effectiveness of home blood pressure telemonitoring: meta-analysis of randomized controlled studies. J Hypertens. 2013;31(3):455–67; discussion 467–8.
61. Parati G, Stergiou G, O'Brien E, Asmar R, Beilin L, Bilo G, et al. European Society of Hypertension practice guidelines for ambulatory blood pressure monitoring. J Hypertens. 2014;32(7):1359–66.
62. McManus RJ, Mant J, Haque MS, Bray EP, Bryan S, Greenfield SM, et al. Effect of self-monitoring and medication self-titration on systolic blood pressure in hypertensive patients at high risk of cardiovascular disease: the TASMIN-SR randomized clinical trial. JAMA. 2014;312(8):799–808.
63. Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, et al. Interventions for enhancing medication adherence. Cochrane Database Syst Rev. 2014;(11):CD000011.
64. Mistry N, Keepanasseril A, Wilczynski NL, Nieuwlaat R, Ravall M, Haynes RB, et al. Technology-mediated interventions for enhancing medication adherence. J Am Med Inform Assoc. 2015;22(e1):e177–93.
65. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. BMJ. 2008;336(7653):1114–7.
66. Christensen A, Osterberg LG, Hansen EH. Electronic monitoring of patient adherence to oral antihypertensive medical treatment: a systematic review. J Hypertens. 2009;27(8):1540–51.
67. Hafezi H, Robertson TL, Moon GD, Au-Yeung K-Y, Zdeblick MJ, Savage GM. An ingestible sensor for measuring medication adherence. IEEE Trans Biomed Eng. 2015;62(1):99–109.
68. Pladevall M, Brotons C, Gabriel R, Arnau A, Suarez C, de la Figuera M, et al. Multicenter cluster-randomized trial of a multifactorial intervention to improve antihypertensive medication adherence and blood pressure control among patients at high cardiovascular risk (the COM99 study). Circulation. 2010;122(12):1183–91.
69. Zeng F, Patel BV, Andrews L, Frech-Tamas F, Rudolph AE. Adherence and persistence of single-pill ARB/CCB combination therapy compared to multiple-pill ARB/CCB regimens. Curr Med Res Opin. 2010;26(12):2877–87.

Drug Adherence with Cardiovascular Medicines: Statins and Aspirin

15

Maarit Jaana Korhonen and Emma Aarnio

15.1 Introduction

Dyslipidemia is a common comorbidity among people with hypertension. Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors or statins have been the mainstay of the management of dyslipidemia during the past three decades. Their efficacy in lowering low-density lipoprotein cholesterol (LDL-C) levels and reducing the risk of cardiovascular events, all-cause and cardiovascular mortality, and need for revascularizations has been convincingly demonstrated [1]. Proportional reductions in major cardiovascular events per mmol/L LDL-C reductions produced by statin therapy seem to be similar in various patient subgroups, including those with or without hypertension.

Joint European Societies' guidelines recommend use of statins depending on the individual's total cardiovascular risk and LDL-C levels [2, 3]. For patients at very high cardiovascular risk (defined as established cardiovascular disease [CVD]; diabetes and complications or ≥1 major risk factor such as hypertension; severe chronic kidney disease; or an estimated 10-year risk of fatal CVD ≥10%), guidelines recommend a LDL-C target of <1.8 mmol/L or, if not achieved, at least a 50%

M. J. Korhonen, Ph.D. (✉)
Institute of Biomedicine, University of Turku, Turku, Finland

Faculty of Pharmacy and Pharmaceutical Sciences, Centre for Medicine Use and Safety, Monash University, Melbourne, VIC, Australia
e-mail: maarit.korhonen@utu.fi

E. Aarnio, Ph.D.
Institute of Biomedicine, University of Turku, Turku, Finland
e-mail: emma.aarnio@utu.fi

M. Burnier (ed.), *Drug Adherence in Hypertension and Cardiovascular Protection*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-76593-8_15

reduction in LDL-C. Lipid-modifying medication is recommended for all patients with myocardial infarction regardless of LDL-C levels and for other very high risk patients with LDL-C levels above the target. For patients with high risk (an estimated 10-year risk of fatal CVD 5%–<10%; markedly elevated single risk factor, e.g., blood pressure ≥ 180/110 mmHg; moderate chronic kidney disease; most other patients with diabetes), medication is recommended if the LDL-C level is above the target value of <2.6 mmol/L.

Also the efficacy of acetylsalicylic acid or aspirin therapy in reducing the risk for fatal and nonfatal cardiovascular events among patients with established atherosclerotic CVD is well documented [4]. Current guidelines recommend that adults with atherosclerotic CVD take low-dose aspirin or other antiplatelet agents as secondary prevention of recurrence of cardiovascular events [2]. In contrast, among primary prevention populations, regardless of presence of hypertension or diabetes, use of aspirin is not recommended because of increased risk of serious bleeding events.

In Europe, prescription rates of statins and aspirin among patients with a recent acute coronary syndrome (ACS) [5–7] and among patients with stable coronary artery disease (CAD) [8] have been high in recent reports. In EUROASPIRE IV, a survey of patients hospitalized for CAD conducted in 24 European countries in 2012–2013, average prescription rates at discharge were 98% for aspirin (or other antiplatelet) and 90% for statins [7]. These rates are higher than for other guideline-recommended secondary prevention medicines, i.e., beta-blockers, and angiotensin converting enzyme inhibitors (ACEI)/angiotensin II receptor blockers (ARB). Almost 40% of patients were prescribed high intensity statin therapy (≥40 mg atorvastatin, ≥20 mg rosuvastatin or specific statin combinations with ezetimibe) [9]. Despite the high prescription rates of lipid-modifying therapy, only one in five patients achieved the guideline-recommended LDL-C target.

Following the changes in guideline recommendations [10], statin use has gradually expanded from secondary prevention in patients with established atherosclerotic CVD to primary prevention in individuals with cardiovascular risk factors [10–12]. For individuals at low to moderate cardiovascular risk, European guidelines recommend a LDL-C goal of <3 mmol/L [2, 3]. However, as in secondary prevention, only a minority of the statin-treated individuals in primary prevention reach the lipid goals. Non-adherence to statins has been shown to greatly affect LDL-C levels [13] and to lead to dose escalation in clinical practice [14]. Thus, non-adherence to or discontinuation of statins is clearly one of the main reasons for inadequate LDL-C lowering in both primary and secondary prevention populations. Similarly, there is evidence that non-adherence could explain nearly half of the cases of so-called aspirin resistance [15].

15.2 Patterns of Non-adherence

Individuals who are prescribed cardiovascular medicines may become non-adherent during different stages of their treatment. Primary non-adherence occurs when new prescriptions are not filled or dispensed medicines are not initiated. Secondary

non-adherence occurs when an initiated medicine is not taken as prescribed or it is discontinued prematurely. Primary adherence, when defined as filling of the initial prescription for a medicine, can only be measured if prescriptions issued to an individual can be captured. The expanding use of electronic prescribing allows for a more complete identification of new prescriptions and when these are matched to dispensation records, estimation of primary non-adherence rates. To date, studies on refill adherence (secondary adherence) have dominated research on adherence to cardiovascular medicines because of readily available pharmacy dispensing or claims data [16]. Adherence to low-dose aspirin is an exception as aspirin is non-reimbursable in many health systems and can also be obtained over the counter. Consequently, the majority of studies have measured adherence to aspirin by self-report [17].

Notwithstanding the variation in adherence measures used, populations and settings studied, non-adherence to cardiovascular medicines is common. Furthermore, it is increasingly recognized that use of cardiovascular medicines is a dynamic process where adherence often declines over time [17] but can also improve in response to acute cardiovascular events [18]. Similarly, discontinuation may be followed by restarting medicine use after shorter or longer periods of time [19–22]. Next, prevalence and incidence of non-adherence to statins and low-dose aspirin at different stages of treatment are discussed.

15.2.1 Initiation and Early Discontinuation

In database studies, primary adherence assesses if a newly issued prescription is dispensed, and early discontinuation assesses if an individual who initiates treatment by having a new prescription dispensed continues the treatment by refilling the prescription. Studies based on closed pharmacy systems have found relatively low primary non-adherence rates (5–8% during the first 4 months) for both statins [23–25] and aspirin [24, 25] among patients hospitalized for an acute cardiovascular event, and for statins also in mixed populations of primary and secondary prevention patients [26, 27]. Despite the use of a longer, 9-month follow-up period, a much higher rate of primary non-adherence (about 40%) to antihypertensive and lipid-lowering medications was reported in a Canadian database study when considering prescriptions for a new indication [28]. Among patients switching to another lipid-lowering medication, the rate was only 8%. Furthermore, database studies indicate that another 10–18% of statin initiators do not fill a second prescription within 1 year following the first prescription [20, 29, 30]. These rates of early discontinuation seem somewhat lower among patients with pre-existing hypertension, coronary heart disease, or diabetes [29–31].

Data from US acute myocardial infarction (AMI) registers collected through patient interviews suggest that the largest drop in use of secondary prevention medicines prescribed at hospital discharge occurs within a month following the discharge [32, 33]. This drop is likely to represent primary non-adherence, or alternatively early discontinuation. In a study of over 6000 patients enrolled in two

AMI registers in 2003–2008, 1 month after discharge on aspirin, statins, beta-blockers, and ACEI/ARB only 50–70% of the patients reported using all prescribed medicines [32]; up to 24% did not use aspirin and up to 30% did not use statin. The highest rates of non-use were observed among patients at highest estimated mortality risk, suggesting that the "treatment-risk paradox," where high-risk patients do not receive guideline-recommended medications, may extend to medication adherence.

15.2.2 Implementation

During the implementation phase, individuals may deviate from the prescribed treatment by taking more or less of their medicine or take it at the wrong time. Dosage regimen for statins and aspirin is typically simple. For example, for statins the instruction is one tablet per day for more than 95% of the patients without specification of timing [34] or to be taken at bedtime [35] which decreases the risk of wrong timing.

Numerous studies have estimated statin adherence based on pharmacy dispensing or claims data and employed proportion measures such as medication possession ratio (MPR) or proportion of days covered (PDC), typically defining non-adherence as MPR/PDC <80% [16, 36]. A meta-analysis of 24 studies including over 600,000 statin users reported an average non-adherence rate of 51% (range 12–76%) at 1 year [36]. When stratifying studies by the study population's prevention status, another meta-analysis of 11 studies with varying follow-up times showed that the average prevalence of non-adherence was much lower in secondary prevention (24%) than in primary prevention populations (43%) [37]. The studies included in the preceding meta-analyses measured adherence by identifying patients filling a first statin prescription and then following claims or dispensation records for subsequent refills. That is, they did not account for primary non-adherence and also assumed that all dispensed medicines are consumed, which leads to overestimation of the proportion of individuals actually taking medicines as prescribed.

In addition to estimating averages of MPR/PDC or rates of non-adherence over a specified time period, other medication taking patterns can be explored using pharmacy refill data. Group-based trajectory modeling (GBTM) can summarize long-term adherence better than the conventional PDC or MPR method as it considers dynamics of adherence over time instead of compressing all the information into a single number for the whole observation period [38]. GBTM is used to identify clusters of individuals with similar adherence patterns and to assign them into groups based on model estimates. Figure 15.1 shows six adherence patterns discerned by GBTM in a Finnish primary prevention cohort during an 18-month follow-up since statin initiation [39]. Based on GBTM, the estimated proportion of those with virtually no dispensations after the first one (trajectory of very rapidly declining adherence) is 16%. This corresponds well to the previously mentioned proportions of individuals with only one prescription fill. The decision on the

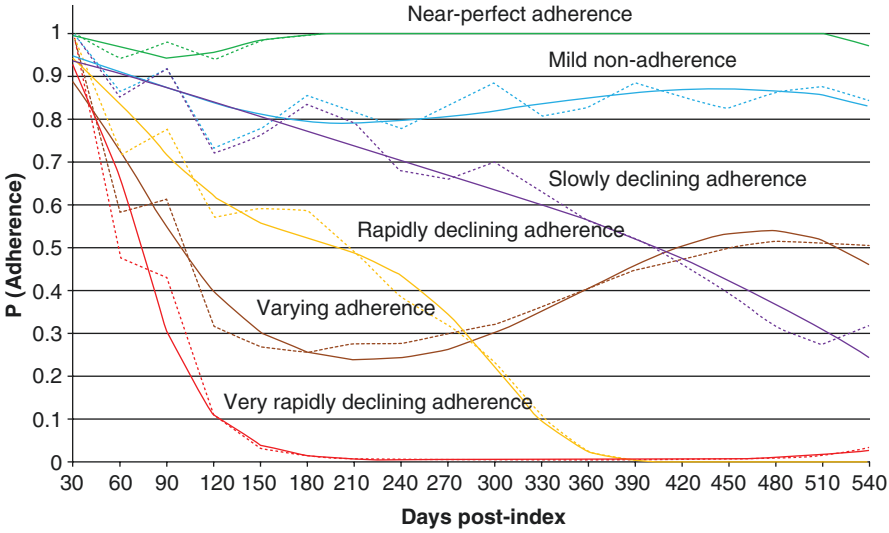


Fig. 15.1 Six statin adherence trajectories identified with group-based trajectory modeling among new Finnish statin users in primary prevention. The solid lines present the predicted probability of adherence and the dashed lines the observed proportion of adherent individuals in each trajectory group. (Modified from [39]. http://circoutcomes.ahajournals.org/content/early/2016/10/18/CIRCOUTCOMES.116.002728)

number of trajectory groups is somewhat arbitrary, and thus the groups identified by GBTM are likely to be model-driven rather than real.

Most of the information on adherence to aspirin comes from older, relatively small studies that have used a variety of adherence measures including self-report [40], electronic monitoring devices [41–43], and biochemical testing to assess pharmacodynamic responses [44]. The estimated rates of non-adherence have ranged widely from about 10% [44] up to almost 50% [40, 45]. A study that assessed adherence to the four guideline-recommended therapies among 208 patients following ACS using the medication adherence scale found similar rates of non-adherence across therapeutic classes; 46% of the patients reported some level of non-adherence to aspirin, typically due to forgetfulness [40]. Two studies measuring adherence with an electronic monitor observed that patients with CAD followed their prescribed twice-a-day aspirin regimen approximately 65–70% of the days during a 3-week observation period [41, 42]. Another study of 172 post-ACS patients measured adherence with a medication event monitoring system over a 3-month period; 23% of the patients were deemed non-adherent (took aspirin <80% of the days as prescribed) [43]. Overall, in patients with established CVD, adherence to low-dose aspirin seems comparable to adherence to statins and antihypertensive medicines [16, 37, 40, 46].

15.2.3 Discontinuation and Reinitiation

Statins, regardless of patient's prevention status, and low-dose aspirin in secondary prevention are purported for lifelong use. Yet patients frequently discontinue these therapies. When measured within the same study, persistence with aspirin therapy has been similar or better than persistence with statins or antihypertensive medicines [5, 6, 33, 40, 47–50]. In studies of patients enrolled in US AMI registers, self-reported 6-month discontinuation rates have ranged from 4 to 26% for aspirin and from 10 to 33% for statins [32, 49, 51], with no discernible further decrease in persistence at 1 year [32]. Surprisingly, similar 1-year discontinuation rates were reported for aspirin (8–16%) and statins (16–23%) by recent European database studies of AMI survivors [5, 6].

An extensive number of studies have focused on persistence with statins [52]. A majority of these studies have employed refill data and adopted the permissible gap method, that is, defined a maximum break between two consecutive refills after which users are deemed to have discontinued treatment. Wide variation in permissible gaps employed (30–365 days) is one reason for large variation in produced estimates. A systematic review on statin persistence among older people reported that median discontinuation rates increased from about one-fourth at year one to almost 40% at year four [52]. Median 1-year discontinuation rate was 24% in primary prevention 17% in secondary prevention.

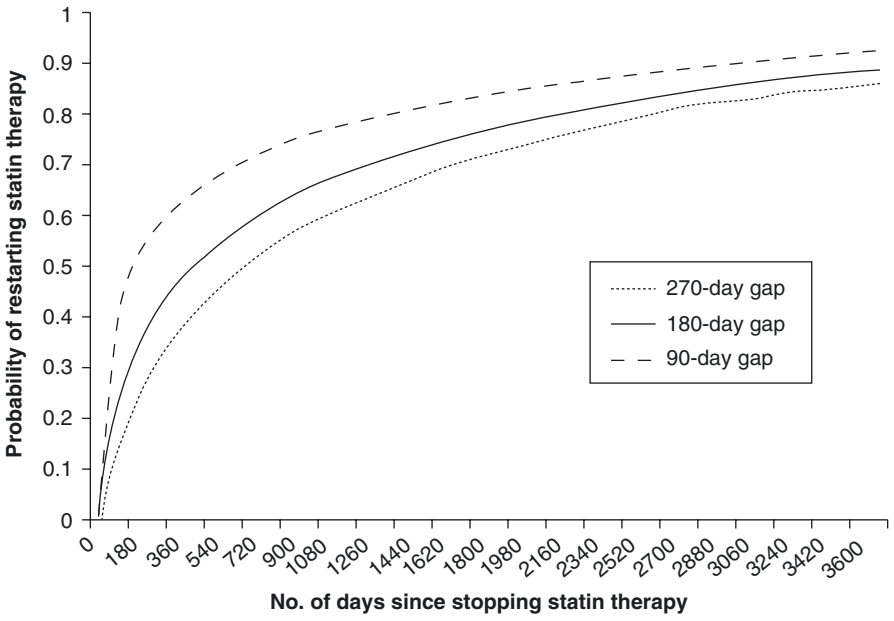


Fig. 15.2 Estimates of probability of restarting statin therapy after discontinuation using a permissible gap of 90, 180, or 270 days. (Reprinted by permission from Springer Nature: Springer lnternational Publishing AG. European Journal of Clinical Pharmacology. Dynamics of long-term statin therapy [20])

A few database studies have demonstrated that a majority of individuals who discontinue statin use reinitiate the use sooner or later [19, 20, 22, 53]. Of over 30,000 Finns who initiated statin use in 1997, almost every second discontinued the use for at least 180 days during the following 10 years; however, about nine in ten discontinuers reinitiated statin use by the end of 2007 (Fig. 15.2) [20]. Only 28% of those who initiated statin use in 2007 had never used statins before. A study of almost 300,000 statin initiators in the UK in 2002–2013 reported discontinuation rates (using a 90-day gap) of 13 and 9.6 per 100 person-years for the primary and secondary prevention patients, respectively. About three in four discontinuers in both prevention groups reinitiated statin use within 2 years after discontinuation [22], similarly to the Finnish cohort [20]. Frequent stopping-restarting of statin use and intermittent use seen among aspirin users [21] may be part of poor implementation or execution of treatment rather than non-persistence.

15.3 Risk Factors for Non-adherence

The reported rates of non-adherence to statins and aspirin vary considerably because of the differences in adherence measures used and populations and settings studied, but this variation is also likely to reflect the multitude and complexity of determinants of non-adherence. This section discusses risk factors for non-adherence to statins and aspirin categorized as factors related to the patient, condition, therapy, and health system, as well as socioeconomic factors, acknowledging the complex interplay among the five categories and individual factors [54]. Table 15.1 lists examples of risk factors for non-adherence found to be associated with non-adherence to statins or aspirin within each of the five categories.

As the rates of non-adherence [16], the general reasons for non-adherence are similar for statins, aspirin, and other cardiovascular medicines. There is an extensive body of literature dealing with predictors of adherence to statins dominated by studies based on administrative healthcare data. In studies aggregating risk factors for non-adherence to those related to the patient, including clinical and sociodemographic characteristics, health system, and payment, factors related to the patient and payment have been found to contribute most to the prediction of statin adherence [63, 65]. However, even when taken together, variables available in administrative databases do not seem to provide useful prediction for adherence [63, 65]. Most importantly, they cannot address patient-reported reasons [70]. As it is the patient who eventually decides whether or not to initiate and continue use of the prescribed medicine, understanding the patient perspective on non-adherence is crucial for any attempt to improve medication adherence.

15.3.1 Patient Factors

Patient-related dimension of non-adherence includes both physical and psychological/behavioral characteristics of the patient [71]. Prevalence of physical risk factors for non-adherence such as visual or cognitive impairment [72] increases with age. However, the associations observed between age and non-adherence to statins and

Table 15.1 Examples of potential risk factors for non-adherence to statins and aspirin

Medicine/category	Risk factors for non-adherence
Statins	
Patient	Lack of perceived necessity for heart medicines [55] Perceived concern about heart medicines [55] Smoking [56] Risky drinking [29, 57, 58]
Condition	Primary prevention [22, 36] Depression [59] Absence of diabetes or hypertension [22, 60] Liver disease [22]
Therapy	Fear or experience of adverse effects [61, 62]
Socioeconomic	High copayment [63] Low socioeconomic status (men) [39] Retirement [64]
Health system	Lack of lipid tests [36] Treatment by a non-cardiologist [65] Lack of patient counseling [61]
Aspirin	
Patient	Female sex [48] Smoking [48, 66]
Condition	Symptomatic angina pectoris [42] Depression [67] Diabetes [48, 66]
Therapy	Experience of adverse effects [68, 69]
Socioeconomic	Being migrant [66] Living in community (vs. long-term care facility) [24]
Health system	Treatment by a non-cardiologist [51]

aspirin have been inconsistent. No robust association between other sociodemographic attributes, such as sex or marital status, and non-adherence has been identified either [17, 36, 63, 73].

Psychological and behavioral factors are among the most important determinants of non-adherence. They include patients' knowledge about their condition, perceived susceptibility to disease, understanding the reason medicine is needed, expectations or attitudes toward treatment, perceived benefit of treatment, motivation, fear of possible adverse effects, frustration with healthcare providers, psychosocial stress, anxiety, and lifestyle-related factors, such as alcohol misuse [71]. Patients' beliefs about the prescribed medicines have been demonstrated to predict adherence after AMI, with those patients with greater perceived necessity of prescribed medicines and lower concerns about adverse effects being less likely to report missing doses of lipid-lowering and other secondary prevention medicines [55]. In addition, patient-reported reasons for discontinuation of post-AMI medicines include the belief that these medicines are not helping with the condition [74]. In a survey of statin-treated patients, the most commonly reported reasons for discontinuing statins were experiences of adverse effects, feeling that treatment was unnecessary, and worry about developing adverse effects [61]. Compared to continuers of statin therapy, discontinuers felt more commonly that statins provided

limited benefit or were unsure of these benefits and less commonly knew that statin therapy would be long-term.

Patient-related reasons for non-adherence are often grouped to intentional and unintentional. Intentional non-adherence is deliberate: patients actively decide not to use their medicine according to recommendations. This is driven by patients' beliefs and experiences [75]. Unintentional non-adherence is more passive and includes, for example, forgetting to take medicines or forgoing medicine use because of low health literacy. Despite the different nature of these two behaviors, also unintentional non-adherence has been linked with patient beliefs. Accordingly, in a US survey among adults with chronic disease (e.g., hyperlipidemia or hypertension), unintentional non-adherence did not appear random and was predicted also by medication beliefs [75].

Unhealthy lifestyle including smoking [56, 76–79], risky drinking [56–58], and clustering of several unhealthy behaviors [58] have predicted non-adherence to lipid-lowering medicines in mixed populations and among patients with established CVD, hypertension, or diabetes. Risky drinkers in particular may intentionally avoid taking their medicine because of potential drug-alcohol interactions, but they may also unintentionally miss doses or even refills due to intoxication, or they may just be less concerned about missing doses [58].

As the use of electronic health records and prescribing is expanding, pharmacists and physicians could use information on individuals' past adherence behavior to identify those individuals at increased risk of future non-adherence. For example, the time elapsed between prescription and dispensing of the initial statin was directly associated with the likelihood of non-adherence during the following year in one study [63]. Another study found that refill adherence to antihypertensive medicines prior to hospitalization for ACS predicted adherence to statins after the event [80]. In fact, past prescription refill behavior may predict adherence better than do patients' prospective health beliefs [81].

15.3.2 Condition

Adherence to medicines used to treat symptomless conditions such as dyslipidemia or to prevent a future adverse event presents a challenge to patients and their physicians. This is no surprise in the light of low adherence rates observed even in the aftermath of acute CVD events [18, 24]. In a US study of older statin users surviving an AMI, the prevalence of non-adherence (PDC < 80%) was even higher (>40%) during the 6 months following the event than before it [18]. However, statin users who were non-adherent prior to the AMI were almost twice as likely to become adherent after it compared to their nonhospitalized counterparts and non-adherent statin users hospitalized for other reasons. That is, for non-adherent medicine users in particular, hospitalization for a cardiovascular event can serve as a teachable moment [82]. This moment could provide clinicians and other health professionals an opportunity for motivating patients to adhere to their medication by pointing out the linkage between the prevention of recurrent events and adherence.

Overall, adherence to statins seems better when patients have a history of CVD or cardiovascular risk factors in addition to elevated LDL-C [22, 30, 36, 60, 83]. Coexisting type 2 diabetes and hypertension have been associated with better statin adherence in primary prevention populations [22, 60]. Furthermore, among individuals free of established CVD, diabetes, and chronic hypertension, overweight and obesity predicted better adherence in one study [58]. Another study found that higher baseline LDL-C levels predicted better persistence with statins among individuals without CVD or diabetes [84]. The preceding observations are consistent with the health belief model positing that individuals' perceived disease risk affects their behavior [85].

Also persistence to aspirin has been linked to the presence of cardiovascular comorbidities, hypertension, or diabetes in a mixed population [21] while presence of diabetes has also predicted less consistent use of aspirin in patients with CAD [48]. Surprisingly, one small study of patients with CAD found that patients reporting symptoms of angina were less adherent to aspirin than patients with silent ischemia [42]. Without the stimulus of immediate improvement in symptoms, symptomatic patients may focus their attention to medicines that provide symptom relief rather than to prophylactic aspirin. One explanation for the observed difference in adherence between patients with symptomatic and silent ischemia is depression which was more common among patients reporting symptoms. Another study that measured adherence to aspirin using the medication event monitoring system reported that over 40% of patients with persistent depressive symptoms were non-adherent (taking aspirin ≤75% of the monitored time) during 3 months after ACS compared to 10% of the patients without depression [67].

Overall, a meta-analysis of US studies on medication adherence among patients with chronic conditions found that patients with depression have almost twice the odds of being non-adherent to cardiovascular medicines compared to their counterparts free of depression [86]. Studies that have measured adherence based on pharmacy records have reported somewhat weaker associations between depression and non-adherence to statins [59, 63, 87, 88]. Among patients with depression, lack of energy, motivation, withdrawal from social contacts, hopelessness, or cognitive changes among other things may contribute to the lack of the readiness and ability to adhere to cardiovascular medicines. Also, post-traumatic stress disorder, common after cardiovascular events, correlates with non-adherence to secondary prevention medicines, independently of depression [89, 90].

The association between anxiety and adherence to preventive therapies is less straightforward as anxiety is a heterogeneous disorder ranging from panic to generalized concern about one's health. Being anxious about one's health and fear of complications of the underlying condition can promote adherence while concerns about potential adverse effects of the medicine can lead to non-adherence [91]. Anxiety has been linked to increased risk of non-adherence to statins and cardiac medicines in studies employing self-reported measures of anxiety [88, 92]. Frequent experiences of somatic symptoms of anxiety such as muscle twitching or chest pain upon anger in particular seem to predict non-adherence to statins [88], potentially due to misattribution of regular physiological reactions to the medicine. In database

studies, diagnosed anxiety disorder or use of anxiolytic medicines has been linked with a decreased risk of non-adherence to statins [93, 94], which suggests that treatment of anxiety might improve adherence.

15.3.3 Therapy

Characteristics of the therapeutic regimen or the medicine itself can affect adherence. The typical "once-daily" dosage regimen for low-dose aspirin and statins is simple. Requirement for more frequent dosing is one likely reason for the reported lower adherence to other lipid-lowering medicines [95]. Nevertheless, a once-daily dosing schedule may lead to non-adherence if it does not match patients' daily routines [35, 81]. For secondary prevention patients, a statin or aspirin is only one of several medicines that must be taken regularly and indefinitely. A post-ACS regimen alone may include up to six distinct medicines. Accordingly, lack of reminder tools (e.g., pillbox) predicted non-adherence after ACS in one study [96]. Among US patients who initiated antihypertensive and lipid-lowering medicines at the same time, adherence to these two therapies was inversely associated with the number of medicines the patient was already taking [97]. Overall, results on the association between the number of medicines in use and non-adherence are mixed and may vary depending on whether medicines considered are for related or unrelated conditions [22, 46]. In fact, the complexities introduced by the health system (e.g., receiving prescriptions from several physicians or filling prescriptions at different pharmacies) may be more important as a risk factor for non-adherence than polypharmacy [98].

Whether it is knowledge, fear, or experience of them, adverse effects are the primary reason for non-adherence to or discontinuation of aspirin [45] or statin therapy [61, 99] given by the patients themselves. Gastroduodenal adverse events associated with aspirin use, including nausea, vomiting, dyspepsia, and bleeding, have been well documented even at the low doses used for cardioprotection [45]. The occurrence of bleeding is dose-dependent but even the low dose (75 mg) doubles the bleeding risk compared to non-use [100]. Estimated proportions of aspirin discontinuation attributed to adverse effects range from less than 10% to almost 50% [45]. A multicenter observational study found that 13% of the patients discontinued use of aspirin during a 3-month follow-up, and those who experienced more than three episodes of gastrointestinal symptoms during the preceding week had a 2.6-fold risk of discontinuation compared to those with no episodes [68].

While statins are considered as among the safest medicines, statin therapy is associated with increased risk of myopathy and diabetes mellitus, and probable excess in hemorrhagic stroke [1]. Observational studies have reported much higher rates of symptoms of statin intolerance or discomfort, particularly muscle-related adverse effects, than have clinical trials, ranging from 10 to 28% among current statin users [61, 62, 101, 102]. Most importantly, 60% of former statin users reported having experienced muscle-related effects and 62% reported adverse effects as the reason for discontinuation of statin treatment in a large internet survey [61]. In a

Finnish survey of over 800 current and former statin users with CAD, chronic hypertension, or diabetes, former users were twice more likely to report concerns of adverse statin effects and four times more likely to report having experienced them compared to current users [62]. Qualitative research on reasons for non-adherence to statins has confirmed the importance of patients' concerns about adverse effects as a key barrier to adherence [99]. Higher statin doses have been associated with higher rates of early discontinuation in some [30] but not all studies [22]. This association may be mediated through experiences of adverse effects.

15.3.4 Socioeconomic Factors

High medication costs or copayment have been consistently identified as predictors of statin non-adherence [36, 63]. However, availability of low-cost aspirin or generic statins, or even full medication coverage does not necessarily remove limited financial resources as a barrier to adherence. When Choudhry et al. [103] evaluated patients given free secondary prevention medicines after AMI, average PDC remained at <60% for statins, beta-blockers, and ACEI/ARB during the 6 months following the event. This observation is supported by a study from Finland, a country with universal healthcare and medication reimbursement systems, which found that the association between low income and non-adherence to statins prescribed for primary prevention in men was not attenuated when patient's out-of-pocket statin costs were considered [39]. Similarly, low income was associated with worse statin adherence despite access to free medical care in a French post-AMI cohort [104].

Retirement is a relevant life transition that can change various aspects of life, such as daily routines, social networks, income, access to healthcare, and, therefore, affect the continuity of care, including medication. Interestingly, retirement has been shown to associate with a substantial decrease in the prevalence of suboptimal health [105]. The perception of fewer symptoms of ill health may lead to a decreased motivation to take medications for a symptomless condition. An increase in non-adherence to and discontinuation of statins was observed after retirement in a large population-based cohort study in Sweden [64]. Increase in the risk of discontinuation was even larger among patients in secondary prevention than among retirees in primary prevention. Therefore, post-retirement increase in non-adherence would be important for healthcare providers to recognize.

15.3.5 Health System and Environmental Factors

Healthcare providers have an important role in adherence to cardiovascular medicines. Frequent contact with healthcare provider and lipid tests soon after initiation have been found to predict better adherence to statins [36, 70]. Continuity of patient–provider relationship is important; in one study, patients' likelihood of resuming statin therapy tripled after a visit with a physician and increased sixfold after a visit with the physician who had written the initial prescription [19]. The

level of expertise that patients are exposed to following an acute event may also play a role as care by a cardiologist rather than a non-specialist has predicted primary adherence to secondary prevention medicines [23] and better persistence to aspirin at 6 months after ACS [51].

Physicians may contribute to non-adherence by prescribing unnecessarily complex regimens and also by failing to explain the benefits and adverse effects of a medicine. Accordingly, in one study, patients with higher persistence with secondary prevention medicines after AMI reported more often that their provider had explained the reasons and potential adverse effects of medicines [49]. Among statin-treated survey respondents, continuers of the therapy reported more commonly being satisfied with physician's counseling than did discontinuers, which also calls for more intensive physician–patient dialogue [61].

Practical issues such as package size and dispensing channels can also affect adherence to cardiovascular medicines. A US study reported that patients obtaining greater quantities of statins at prescription fills (60-day vs. 30-day supplies) were more likely to be adherent and also have lower LDL-C levels [106]. Another US study found that home delivery of medicines predicted better adherence to antihypertensive, antidiabetic, and lipid-modifying medicines compared to filling prescriptions using retail channels [107]. Filling of prescriptions may be simply too burdensome for some patients, leading to non-adherence.

More distal factors beyond the health system may affect adherence to cardiovascular medicines. Negative media coverage is an example of environmental factors that may affect public perceptions of safety and effectiveness of medicines. Studies from different countries have demonstrated increases in rates of discontinuation of statin therapy following negative news stories [30, 108, 109]. Most importantly, increases in discontinuation were seen in both primary and secondary prevention populations [108, 109]. These observations accord with those from a patient survey in Finland where almost 30% of statin discontinuers with CAD, hypertension, or diabetes gave public discussion about adverse effects as the reason for discontinuing the therapy [62]. In Denmark, the negative nationwide statin-related news stories were estimated to have translated to a 2% increase in the risk of myocardial infarction through increased discontinuation [30]. Identifying the information sources patients use to learn about medicines and stressing the benefits of the therapy at the time of prescribing and discussion of potential adverse effects and their incidence and seriousness may influence how patients filter information from these sources. As many patients seem to discontinue medicine use without consulting healthcare providers [61, 62], tackling non-adherence to cardiovascular medicines may require broader action involving researchers, the academic press, and lay media in addition to the health system.

Conclusions

Adherence to statins and aspirin is undeniably a complex behavioral process affected also by the broader environment in which people live, and healthcare providers and systems operate. Whatever the reasons are, non-adherence to these medicines is prevalent and has been demonstrated to lead to worse health outcomes, such as increased risk of CVD events and mortality [16, 110] and higher

healthcare costs [110]. Adherence to evidence-based cardiovascular medicines needs improvement but this process has to face the complexity of the phenomenon itself and the numerous factors affecting it.

References

1. Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet. 2016;388(10059):2532–61.
2. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016;37(29):2315–81.
3. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias: the Task Force for the Management of Dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Atherosclerosis. 2016;253:281–344.
4. Antithrombotic Trialists Collaboration, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009;373(9678):1849–60.
5. Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M, Janzon M. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. Eur Heart J. 2015;36(19):1163–70.
6. Halvorsen S, Jortveit J, Hasvold P, Thuresson M, Oie E. Initiation of and long-term adherence to secondary preventive drugs after acute myocardial infarction. BMC Cardiovasc Disord. 2016;16:115.
7. Kotseva K, Wood D, De Bacquer D, De Backer G, Ryden L, Jennings C, et al. EUROASPIRE IV: a European Society of Cardiology survey on the lifestyle, risk factor and therapeutic management of coronary patients from 24 European countries. Eur J Prev Cardiol. 2016;23(6):636–48.
8. Ferrari R, Ford I, Greenlaw N, Tardif JC, Tendera M, Abergel H, et al. Geographical variations in the prevalence and management of cardiovascular risk factors in outpatients with CAD: data from the contemporary CLARIFY registry. Eur J Prev Cardiol. 2015;22(8):1056–65.
9. Reiner Z, De Backer G, Fras Z, Kotseva K, Tokgozoglu L, Wood D, et al. Lipid lowering drug therapy in patients with coronary heart disease from 24 European countries—findings from the EUROASPIRE IV survey. Atherosclerosis. 2016;246:243–50.
10. Wallach Kildemoes H, Vass M, Hendriksen C, Andersen M. Statin utilization according to indication and age: a Danish cohort study on changing prescribing and purchasing behaviour. Health Policy. 2012;108(2–3):216–27.
11. Rikala M, Huupponen R, Helin-Salmivaara A, Korhonen MJ. Channelling of statin use towards low-risk population and patients with diabetes. Basic Clin Pharmacol Toxicol. 2013;113(3):173–8.
12. van Staa TP, Smeeth L, Ng ES, Goldacre B, Gulliford M. The efficiency of cardiovascular risk assessment: do the right patients get statin treatment? Heart. 2013;99(21):1597–602.
13. Shalev V, Goldshtein I, Halpern Y, Chodick G. Association between persistence with statin therapy and reduction in low-density lipoprotein cholesterol level: analysis of real-life data from community settings. Pharmacotherapy. 2014;34(1):1–8.

14. Pittman DG, Fenton C, Chen W, Haffner S, Pendergrass M. Relation of statin nonadherence and treatment intensification. Am J Cardiol. 2012;110(10):1459–63.
15. Dawson J, Quinn T, Rafferty M, Higgins P, Ray G, Lees KR, et al. Aspirin resistance and compliance with therapy. Cardiovasc Ther. 2011;29(5):301–7.
16. Chowdhury R, Khan H, Heydon E, Shroufi A, Fahimi S, Moore C, et al. Adherence to cardiovascular therapy: a meta-analysis of prevalence and clinical consequences. Eur Heart J. 2013;34(38):2940–8.
17. Duffy D, Kelly E, Trang A, Whellan D, Mills G. Aspirin for cardioprotection and strategies to improve patient adherence. Postgrad Med. 2014;126(1):18–28.
18. Kronish IM, Ross JS, Zhao H, Muntner P. Impact of hospitalization for acute myocardial infarction on adherence to statins among older adults. Circ Cardiovasc Qual Outcomes. 2016;9(4):364–71.
19. Brookhart MA, Patrick AR, Schneeweiss S, Avorn J, Dormuth C, Shrank W, et al. Physician follow-up and provider continuity are associated with long-term medication adherence: a study of the dynamics of statin use. Arch Intern Med. 2007;167(8):847–52.
20. Korhonen MJ, Helin-Salmivaara A, Huupponen R. Dynamics of long-term statin therapy. Eur J Clin Pharmacol. 2011;67(9):925–31.
21. Filippi A, Bianchi C, Parazzini F, Cricelli C, Sessa E, Mazzaglia G. A national survey on aspirin patterns of use and persistence in community outpatients in Italy. Eur J Cardiovasc Prev Rehabil. 2011;18(5):695–703.
22. Vinogradova Y, Coupland C, Brindle P, Hippisley-Cox J. Discontinuation and restarting in patients on statin treatment: prospective open cohort study using a primary care database. BMJ. 2016;353:i3305.
23. Jackevicius CA, Li P, Tu JV. Prevalence, predictors, and outcomes of primary nonadherence after acute myocardial infarction. Circulation. 2008;117(8):1028–36.
24. Glader EL, Sjolander M, Eriksson M, Lundberg M. Persistent use of secondary preventive drugs declines rapidly during the first 2 years after stroke. Stroke. 2010;41(2):397–401.
25. Ullberg T, Glader EL, Zia E, Petersson J, Eriksson M, Norrving B. Associations between ischemic stroke follow-up, socioeconomic status, and adherence to secondary preventive drugs in southern Sweden: observations from the Swedish stroke register (Riksstroke). Neuroepidemiology. 2017;48(1–2):32–8.
26. Pottegard A, Christensen R, Houji A, Christiansen CB, Paulsen MS, Thomsen JL, et al. Primary non-adherence in general practice: a Danish register study. Eur J Clin Pharmacol. 2014;70(6):757–63.
27. Thengilsdottir G, Pottegard A, Linnet K, Halldorsson M, Almarsdottir AB, Gardarsdottir H. Do patients initiate therapy? Primary non-adherence to statins and antidepressants in Iceland. Int J Clin Pract. 2015;69(5):597–603.
28. Tamblyn R, Eguale T, Huang A, Winslade N, Doran P. The incidence and determinants of primary nonadherence with prescribed medication in primary care: a cohort study. Ann Intern Med. 2014;160(7):441–50.
29. Halava H, Huupponen R, Pentti J, Kivimaki M, Vahtera J. Predictors of first-year statin medication discontinuation: a cohort study. J Clin Lipidol. 2016;10(4):987–95.
30. Nielsen SF, Nordestgaard BG. Negative statin-related news stories decrease statin persistence and increase myocardial infarction and cardiovascular mortality: a nationwide prospective cohort study. Eur Heart J. 2016;37(11):908–16.
31. Lemstra M, Blackburn D. Nonadherence to statin therapy: discontinuation after a single fill. Can J Cardiol. 2012;28(5):567–73.
32. Shore S, Jones PG, Maddox TM, Bradley SM, Stolker JM, Arnold SV, et al. Longitudinal persistence with secondary prevention therapies relative to patient risk after myocardial infarction. Heart. 2015;101(10):800–7.
33. Ho PM, Spertus JA, Masoudi FA, Reid KJ, Peterson ED, Magid DJ, et al. Impact of medication therapy discontinuation on mortality after myocardial infarction. Arch Intern Med. 2006;166(17):1842–7.

34. Romppainen T, Rikala M, Aarnio E, Korhonen MJ, Saastamoinen LK, Huupponen R. Measurement of statin exposure in the absence of information on prescribed doses. Eur J Clin Pharmacol. 2014;70(10):1275–6.
35. Martin-Latry K, Cazaux J, Lafitte M, Couffinhal T. Negative impact of physician prescribed drug dosing schedule requirements on patient adherence to cardiovascular drugs. Pharmacoepidemiol Drug Saf. 2014;23(10):1088–92.
36. Lemstra M, Blackburn D, Crawley A, Fung R. Proportion and risk indicators of nonadherence to statin therapy: a meta-analysis. Can J Cardiol. 2012;28(5):574–80.
37. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. Am J Med. 2012;125(9):882–7.e1.
38. Franklin JM, Shrank WH, Pakes J, Sanfelix-Gimeno G, Matlin OS, Brennan TA, et al. Group-based trajectory models: a new approach to classifying and predicting long-term medication adherence. Med Care. 2013;51(9):789–96.
39. Aarnio E, Martikainen J, Winn AN, Huupponen R, Vahtera J, Korhonen MJ. Socioeconomic inequalities in statin adherence under universal coverage: does sex matter? Circ Cardiovasc Qual Outcomes. 2016;9(6):704–13.
40. Sud A, Kline-Rogers EM, Eagle KA, Fang J, Armstrong DF, Rangarajan K, et al. Adherence to medications by patients after acute coronary syndromes. Ann Pharmacother. 2005;39(11):1792–7.
41. Carney RM, Freedland KE, Eisen SA, Rich MW, Jaffe AS. Major depression and medication adherence in elderly patients with coronary artery disease. Health Psychol. 1995;14(1):88–90.
42. Carney RM, Freedland KE, Eisen SA, Rich MW, Skala JA, Jaffe AS. Adherence to a prophylactic medication regimen in patients with symptomatic versus asymptomatic ischemic heart disease. Behav Med. 1998;24(1):35–9.
43. Rieckmann N, Gerin W, Kronish IM, Burg MM, Chaplin WF, Kong G, et al. Course of depressive symptoms and medication adherence after acute coronary syndromes: an electronic medication monitoring study. J Am Coll Cardiol. 2006;48(11):2218–22.
44. Lago A, Tembl JI, Pareja A, Ponz A, Ferrer JM, Valles J, et al. Adherence to aspirin in secondary prevention of ischemic stroke. Cerebrovasc Dis. 2006;21(5–6):353–6.
45. Herlitz J, Toth PP, Naesdal J. Low-dose aspirin therapy for cardiovascular prevention: quantification and consequences of poor compliance or discontinuation. Am J Cardiovasc Drugs. 2010;10(2):125–41.
46. Hamood H, Hamood R, Green MS, Almog R. Determinants of adherence to evidence-based therapy after acute myocardial infarction. Eur J Prev Cardiol. 2016;23(9):975–85.
47. Kulkarni SP, Alexander KP, Lytle B, Heiss G, Peterson ED. Long-term adherence with cardiovascular drug regimens. Am Heart J. 2006;151(1):185–91.
48. Newby LK, LaPointe NM, Chen AY, Kramer JM, Hammill BG, DeLong ER, et al. Long-term adherence to evidence-based secondary prevention therapies in coronary artery disease. Circulation. 2006;113(2):203–12.
49. Mathews R, Wang TY, Honeycutt E, Henry TD, Zettler M, Chang M, et al. Persistence with secondary prevention medications after acute myocardial infarction: insights from the TRANSLATE-ACS study. Am Heart J. 2015;170(1):62–9.
50. Murphy SJ, Coughlan CA, Tobin O, Kinsella J, Lonergan R, Gutkin M, et al. Continuation and adherence rates on initially-prescribed intensive secondary prevention therapy after Rapid Access Stroke Prevention (RASP) service assessment. J Neurol Sci. 2016;361:13–8.
51. Eagle KA, Kline-Rogers E, Goodman SG, Gurfinkel EP, Avezum A, Flather MD, et al. Adherence to evidence-based therapies after discharge for acute coronary syndromes: an ongoing prospective, observational study. Am J Med. 2004;117(2):73–81.
52. Ofori-Asenso R, Jakhu A, Curtis AJ, Zomer E, Korhonen MJ, Nelson M, Gambhir M, Tonkin A, Liew D, Zoungas S. Adherence and persistence among statin users aged 65 years and over: a systematic review and meta-analysis. J Gerontol A Biol Sci Med Sci. 2017. https://doi.org/10.1093/gerona/glx169017.

53. Zhang H, Plutzky J, Skentzos S, Morrison F, Mar P, Shubina M, et al. Discontinuation of statins in routine care settings: a cohort study. Ann Intern Med. 2013;158(7):526–34.
54. Sabate E. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization; 2003.
55. Allen LaPointe NM, Ou FS, Calvert SB, Melloni C, Stafford JA, Harding T, et al. Association between patient beliefs and medication adherence following hospitalization for acute coronary syndrome. Am Heart J. 2011;161(5):855–63.
56. Warren JR, Falster MO, Fox D, Jorm L. Factors influencing adherence in long-term use of statins. Pharmacoepidemiol Drug Saf. 2013;22(12):1298–307.
57. Bryson CL, Au DH, Sun H, Williams EC, Kivlahan DR, Bradley KA. Alcohol screening scores and medication nonadherence. Ann Intern Med. 2008;149(11):795–804.
58. Halava H, Korhonen MJ, Huupponen R, Setoguchi S, Pentti J, Kivimaki M, et al. Lifestyle factors as predictors of nonadherence to statin therapy among patients with and without cardiovascular comorbidities. CMAJ. 2014;186(12):E449–56.
59. Tuppin P, Neumann A, Danchin N, de Peretti C, Weill A, Ricordeau P, et al. Evidence-based pharmacotherapy after myocardial infarction in France: adherence-associated factors and relationship with 30-month mortality and rehospitalization. Arch Cardiovasc Dis. 2010;103(6–7):363–75.
60. Mann DM, Woodward M, Muntner P, Falzon L, Kronish I. Predictors of nonadherence to statins: a systematic review and meta-analysis. Ann Pharmacother. 2010;44(9):1410–21.
61. Cohen JD, Brinton EA, Ito MK, Jacobson TA. Understanding Statin Use in America and Gaps in Patient Education (USAGE): an internet-based survey of 10,138 current and former statin users. J Clin Lipidol. 2012;6(3):208–15.
62. Silvennoinen R, Turunen JH, Kovanen PT, Syvanne M, Tikkanen MJ. Attitudes and actions: a survey to assess statin use among Finnish patients with increased risk for cardiovascular events. J Clin Lipidol. 2017;11(2):485–94.
63. Aarnio EJ, Martikainen JA, Helin-Salmivaara A, Huupponen RK, Hartikainen JE, Peura PK, et al. Register-based predictors of adherence among new statin users in Finland. J Clin Lipidol. 2014;8(1):117–25.
64. Halava H, Westerlund H, Korhonen MJ, Pentti J, Kivimaki M, Kjeldgard L, et al. Influence of retirement on adherence to statins in the insurance medicine all-Sweden total population data base. PLoS One. 2015;10(6):e0130901.
65. Chan DC, Shrank WH, Cutler D, Jan S, Fischer MA, Liu J, et al. Patient, physician, and payment predictors of statin adherence. Med Care. 2010;48(3):196–202.
66. Cuisset T, Quilici J, Fugon L, Cohen W, Roux P, Gaborit B, et al. Non-adherence to aspirin in patients undergoing coronary stenting: negative impact of comorbid conditions and implications for clinical management. Arch Cardiovasc Dis. 2011;104(5):306–12.
67. Rieckmann N, Kronish IM, Haas D, Gerin W, Chaplin WF, Burg MM, et al. Persistent depressive symptoms lower aspirin adherence after acute coronary syndromes. Am Heart J. 2006;152(5):922–7.
68. Pratt S, Thompson VJ, Elkin EP, Naesdal J, Sorstadius E. The impact of upper gastrointestinal symptoms on nonadherence to, and discontinuation of, low-dose acetylsalicylic acid in patients with cardiovascular risk. Am J Cardiovasc Drugs. 2010;10(5):281–8.
69. Moberg C, Naesdal J, Svedberg LE, Duchateau D, Harte N. Impact of gastrointestinal problems on adherence to low-dose acetylsalicylic Acid: a quantitative study in patients with cardiovascular risk. Patient. 2011;4(2):103–13.
70. McGinnis B, Olson KL, Magid D, Bayliss E, Korner EJ, Brand DW, et al. Factors related to adherence to statin therapy. Ann Pharmacother. 2007;41(11):1805–11.
71. American Society on Aging and American Society of Consultant Pharmacists Foundation. Adult Meducation American Society on Aging and American Society of Consultant Pharmacists Foundation; 2012. http://www.adultmeducation.com.
72. Stilley CS, Sereika S, Muldoon MF, Ryan CM, Dunbar-Jacob J. Psychological and cognitive function: predictors of adherence with cholesterol lowering treatment. Ann Behav Med. 2004;27(2):117–24.

73. Maningat P, Gordon BR, Breslow JL. How do we improve patient compliance and adherence to long-term statin therapy? Curr Atheroscler Rep. 2013;15(1):291.
74. Ali RC, Melloni C, Ou FS, Schmader K, Ohman EM, Roe MT, et al. Age and persistent use of cardiovascular medication after acute coronary syndrome: results from medication applied and sustained over time. J Am Geriatr Soc. 2009;57(11):1990–6.
75. Gadkari AS, McHorney CA. Unintentional non-adherence to chronic prescription medications: how unintentional is it really? BMC Health Serv Res. 2012;12:98.
76. Kopjar B, Sales AE, Pineros SL, Sun H, Li YF, Hedeen AN. Adherence with statin therapy in secondary prevention of coronary heart disease in veterans administration male population. Am J Cardiol. 2003;92(9):1106–8.
77. Yang CC, Jick SS, Testa MA. Discontinuation and switching of therapy after initiation of lipid-lowering drugs: the effects of comorbidities and patient characteristics. Br J Clin Pharmacol. 2003;56(1):84–91.
78. Di Martino M, Degli Esposti L, Ruffo P, Bustacchini S, Catte A, Sturani A, et al. Underuse of lipid-lowering drugs and factors associated with poor adherence: a real practice analysis in Italy. Eur J Clin Pharmacol. 2005;61(3):225–30.
79. Carey IM, DeWilde S, Shah SM, Harris T, Whincup PH, Cook DG. Statin use after first myocardial infarction in UK men and women from 1997 to 2006: who started and who continued treatment? Nutr Metab Cardiovasc Dis. 2012;22(5):400–8.
80. Muntner P, Yun H, Sharma P, Delzell E, Kent ST, Kilgore ML, et al. Ability of low antihypertensive medication adherence to predict statin discontinuation and low statin adherence in patients initiating treatment after a coronary event. Am J Cardiol. 2014;114(6):826–31.
81. Molfenter TD, Bhattacharya A, Gustafson DH. The roles of past behavior and health beliefs in predicting medication adherence to a statin regimen. Patient Prefer Adherence. 2012;6:643–51.
82. McBride CM, Emmons KM, Lipkus IM. Understanding the potential of teachable moments: the case of smoking cessation. Health Educ Res. 2003;18(2):156–70.
83. Latry P, Molimard M, Dedieu B, Couffinhal T, Begaud B, Martin-Latry K. Adherence with statins in a real-life setting is better when associated cardiovascular risk factors increase: a cohort study. BMC Cardiovasc Disord. 2011;11:46.
84. Citarella A, Linder M, Kieler H, Berglind IA, Sundstrom A, Wettermark B, et al. Influence of baseline low-density lipoprotein cholesterol values on statin therapy persistence. Eur J Clin Pharmacol. 2016;72(3):349–57.
85. Elder JP, Ayala GX, Harris S. Theories and intervention approaches to health-behavior change in primary care. Am J Prev Med. 1999;17(4):275–84.
86. Grenard JL, Munjas BA, Adams JL, Suttorp M, Maglione M, McGlynn EA, et al. Depression and medication adherence in the treatment of chronic diseases in the United States: a meta-analysis. J Gen Intern Med. 2011;26(10):1175–82.
87. Benner JS, Glynn RJ, Mogun H, Neumann PJ, Weinstein MC, Avorn J. Long-term persistence in use of statin therapy in elderly patients. JAMA. 2002;288(4):455–61.
88. Korhonen MJ, Pentti J, Hartikainen J, Kivimaki M, Vahtera J. Somatic symptoms of anxiety and nonadherence to statin therapy. Int J Cardiol. 2016;214:493–9.
89. Shemesh E, Yehuda R, Milo O, Dinur I, Rudnick A, Vered Z, et al. Posttraumatic stress, nonadherence, and adverse outcome in survivors of a myocardial infarction. Psychosom Med. 2004;66(4):521–6.
90. Kronish IM, Edmondson D, Goldfinger JZ, Fei K, Horowitz CR. Posttraumatic stress disorder and adherence to medications in survivors of strokes and transient ischemic attacks. Stroke. 2012;43(8):2192–7.
91. Thunander Sundbom L, Bingefors K. Women and men report different behaviours in, and reasons for medication non-adherence: a nationwide Swedish survey. Pharm Pract (Granada). 2012;10(4):207–21.
92. Dempe C, Junger J, Hoppe S, Katzenberger ML, Moltner A, Ladwig KH, et al. Association of anxious and depressive symptoms with medication nonadherence in patients with stable coronary artery disease. J Psychosom Res. 2013;74(2):122–7.

93. Perreault S, Blais L, Dragomir A, Bouchard MH, Lalonde L, Laurier C, et al. Persistence and determinants of statin therapy among middle-aged patients free of cardiovascular disease. Eur J Clin Pharmacol. 2005;61(9):667–74.
94. Perreault S, Blais L, Lamarre D, Dragomir A, Berbiche D, Lalonde L, et al. Persistence and determinants of statin therapy among middle-aged patients for primary and secondary prevention. Br J Clin Pharmacol. 2005;59(5):564–73.
95. Bae JP, Dobesh PP, Klepser DG, Anderson JD, Zagar AJ, McCollam PL, et al. Adherence and dosing frequency of common medications for cardiovascular patients. Am J Manag Care. 2012;18(3):139–46.
96. Melloni C, Alexander KP, Ou FS, LaPointe NM, Roe MT, Newby LK, et al. Predictors of early discontinuation of evidence-based medicine after acute coronary syndrome. Am J Cardiol. 2009;104(2):175–81.
97. Benner JS, Chapman RH, Petrilla AA, Tang SS, Rosenberg N, Schwartz JS. Association between prescription burden and medication adherence in patients initiating antihypertensive and lipid-lowering therapy. Am J Health Syst Pharm. 2009;66(16):1471–7.
98. Choudhry NK, Fischer MA, Avorn J, Liberman JN, Schneeweiss S, Pakes J, et al. The implications of therapeutic complexity on adherence to cardiovascular medications. Arch Intern Med. 2011;171(9):814–22.
99. Fung V, Sinclair F, Wang H, Dailey D, Hsu J, Shaber R. Patients' perspectives on nonadherence to statin therapy: a focus-group study. Perm J. 2010;14(1):4–10.
100. Park K, Bavry AA. Aspirin: its risks, benefits, and optimal use in preventing cardiovascular events. Cleve Clin J Med. 2013;80(5):318–26.
101. Rosenbaum D, Dallongeville J, Sabouret P, Bruckert E. Discontinuation of statin therapy due to muscular side effects: a survey in real life. Nutr Metab Cardiovasc Dis. 2013;23(9):871–5.
102. Stroes ES, Thompson PD, Corsini A, Vladutiu GD, Raal FJ, Ray KK, et al. Statin-associated muscle symptoms: impact on statin therapy-European Atherosclerosis Society Consensus Panel Statement on Assessment, Aetiology and Management. Eur Heart J. 2015;36(17):1012–22.
103. Choudhry NK, Avorn J, Glynn RJ, Antman EM, Schneeweiss S, Toscano M, et al. Full coverage for preventive medications after myocardial infarction. N Engl J Med. 2011;365(22):2088–97.
104. Danchin N, Neumann A, Tuppin P, De Peretti C, Weill A, Ricordeau P, et al. Impact of free universal medical coverage on medical care and outcomes in low-income patients hospitalized for acute myocardial infarction: an analysis from the FrenchNational Health Insurance system. Circ Cardiovasc Qual Outcomes. 2011;4(6):619–25.
105. Westerlund H, Kivimaki M, Singh-Manoux A, Melchior M, Ferrie JE, Pentti J, et al. Self-rated health before and after retirement in France (GAZEL): a cohort study. Lancet. 2009;374(9705):1889–96.
106. Batal HA, Krantz MJ, Dale RA, Mehler PS, Steiner JF. Impact of prescription size on statin adherence and cholesterol levels. BMC Health Serv Res. 2007;7:175.
107. Iyengar RN, LeFrancois AL, Henderson RR, Rabbitt RM. Medication nonadherence among Medicare beneficiaries with comorbid chronic conditions: influence of pharmacy dispensing channel. J Manag Care Spec Pharm. 2016;22(5):550–60.
108. Matthews A, Herrett E, Gasparrini A, Van Staa T, Goldacre B, Smeeth L, et al. Impact of statin related media coverage on use of statins: interrupted time series analysis with UK primary care data. BMJ. 2016;353:i3283.
109. Bezin J, Francis F, Nguyen NV, Robinson P, Blin P, Fourrier-Reglat A, et al. Impact of a public media event on the use of statins in the French population. Arch Cardiovasc Dis. 2017;110(2):91–8.
110. Bitton A, Choudhry NK, Matlin OS, Swanton K, Shrank WH. The impact of medication adherence on coronary artery disease costs and outcomes: a systematic review. Am J Med. 2013;126(4):357.e7–e27.

Which Interventions Are Useful?

16

Todd Ruppar

The number of studies testing interventions to improve adherence to medications is currently in the thousands. The overall impact of adherence intervention trials has shown that it is possible to improve medication adherence, but some interventions are more effective than others [1–4]. Intervention effectiveness will vary based on patients' individual situations and needs. While it would be nice to have a single intervention or intervention program that would improve medication adherence for all patients, this approach does not fit the reality of diverse patient populations. No single intervention will be effective for all patients [1, 2].

Interventions have also not shown a consistent impact on improving clinical outcomes, even when the intervention is successful at improving adherence behavior [4]. The reasons for this are unclear and may be due to multiple factors. For instance, it is possible that the improvement in adherence is still too small to have an effect on the associated clinical outcome. Another possibility, and possibly more likely, is that there are many factors which influence change in clinical outcomes (blood pressure is a good example of this), and controlling for the many different factors influencing the clinical outcome is a major methodological challenge in adherence intervention trials. For the purpose of this chapter, we will focus on medication adherence behavior as the outcome, since clinical outcomes will vary by health condition and are subject to more outside influences.

Adherence intervention studies tend not to specify which aspect of the adherence process the intervention seeks to improve. Adherence to medications occurs along a continuum, from filling the prescription and taking the first dose (initiation), to correctly taking each dose (implementation), and continuing to take the medication for

T. Ruppar, Ph.D., R.N., F.A.H.A.
Rush University College of Nursing, Chicago, IL, USA
e-mail: todd_ruppar@rush.edu, ruppart@missouri.edu

M. Burnier (ed.), *Drug Adherence in Hypertension and Cardiovascular Protection*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-76593-8_16

as long as it is indicated (persistence) [5]. When choosing adherence interventions to recommend to patients, it is important to be mindful of which phase of the adherence process the patient will need help with at any given time.

16.1 Type of Nonadherence

To maximize intervention effectiveness, it is also important to ensure that the intervention is addressing the patient's reasons for nonadherence. In particular, interventionists must consider whether a patient's nonadherence is intentional or unintentional, as the intervention approach will necessarily be quite different.

16.1.1 Unintentional Nonadherence

Unintentional nonadherence will occur when a patient plans to adhere to their medication regimen, but struggles to remember to take their medications or has other barriers to achieving good adherence (e.g., poor access to a pharmacy, inability to afford medications). Of interventions tested to date, the most effective interventions are those addressing unintentional nonadherence [1, 4].

For patients who simply struggle to remember to take their medication, a combination of reminders and pillboxes are useful, inexpensive interventions [6]. Reminders, such as phone alarms, visual cues in their home environment, or some other method, can be used to provide a reliable method of reminding a patient to take his or her medication, although reminders are not effective for all patients [7].

Pillboxes and blister packs each provide a mechanism for the patient to see whether he or she has taken a particular dose of their medication [6]. Often, patients may not recall if they have taken their medication, so having some form of monitoring or dose-by-dose feedback enables patients to reliably know whether a dose was taken. For pillboxes and blister packs, it is as simple as seeing if the pill for that dose is still in the package or not. Other patients use a medication log or diary to record their medication-taking. Logs and diaries have been shown to be effective, but they require more proactive effort on the part of the patient [8]. Pillboxes and blister packs require less effort with each dose to track medication-taking behavior.

Although blister packs are more expensive than weekly pillboxes, blister packs are typically prepared by a pharmacist and do not require the patient or caregiver to set up the packaging. This improves the likelihood that the packaging method will be used to improve adherence, and is also quite useful when patients may struggle to set up a pillbox due to functional or cognitive impairment.

Environmental cues and reminders are visual or auditory triggers that can be useful to help prompt patients to remember medication or to take a medication at a given time. Such reminder systems should be systems that the patient can "set and forget" but not be so annoying that the patient will turn it off, which tends to happen with many beeping alarms. Patients should be encouraged to find a reminder system that will be effective for them, and which they can live with without the reminder

becoming an annoyance. Reminder systems do not need to be alarms, however. A reminder could be a note on or next to a daily calendar, or on a refrigerator—something in the patient's environment that they will see regularly to serve as a reminder to take medications.

Instead of relying on alarms and active cues, interventions that seek to integrate medication-taking into daily habits and routines show promise in improving adherence behavior [1]. These types of interventions help patients to associate medication-taking with other daily habits that the patient will not forget to do, so that medication-taking is also not forgotten. This then ensures that medication adherence does not rely on an alarm reminder or some other device that may fail or must be set by the patient, but rather helps the medication-taking to become a routine habit.

Habit formation as an intervention approach has been shown to be particularly successful when done using a personal systems improvement approach, running small trial "experiments" of how to improve their medication-taking behavior until a method is found that works for the patient [9]. This approach allows patients to look at factors that might help or hinder the patient in remembering and taking medications.

Self-monitoring has also been shown to be effective, but requires sufficient self-discipline from the patient [8]. Self-monitoring interventions involve the patient keeping a log or diary of their medication-taking behavior. Medication logs can be pen and paper or electronic; many apps are now available to facilitate tracking medication-taking on smartphones. Some apps have the option to link with electronic health records to send the log to the patient's health care provider.

Passive monitoring, such as from electronic monitoring devices, reduces the work on the patient when compared to self-monitoring. As an objective measure of adherence behavior, passive monitoring can also show patients how they are actually doing with taking their medication, which many patients find surprising. Patients often think they are more adherent to their medication regimens than they actually are. Passive monitoring devices can be useful when working with patients to make changes to improve medication-taking behavior, as such monitoring provides objective measurement of medication adherence to use to evaluate the effectiveness of whatever behavior and/or lifestyle changes have been tried.

16.1.2 Intentional Nonadherence

Intentional nonadherence is a more difficult type of medication nonadherence to improve. Changing intentional nonadherence requires a careful assessment of why the patient has decided to change or stop his or her medication regimen. The reasons may be something as straightforward as problematic side effects, or as complicated as distrust of the health care provider or erroneous beliefs about one's health condition or treatment regimen [10].

Interventions for intentional nonadherence have not been studied as extensively as unintentional nonadherence interventions. Most tested interventions have relied

on patient education approaches, which tend to be ineffective overall [1, 8]. While patients need to receive adequate information about their medication regimens to be able to take the medication correctly, education alone seldom changes behavior. Some recent trials have shown promising efficacy from interventions using motivational interviewing, which goes beyond basic medication education to work toward addressing the reasons for intentional nonadherence [11, 12].

16.2 General Approaches

Reducing medication regimen complexity may help improve both intentional and unintentional nonadherence. Taking medication fewer times per day is associated with greater adherence, thus reducing regimen complexity may help patients to adhere to their medication regimens [13]. There is also a growing body of literature supporting the "deprescribing" approach, where medications are reviewed and nonessential medications are discontinued. This serves to both reduce regimen complexity and reassure the patient that their health care provider is ensuring that the patient is not taking unnecessary medication [14]. Involving the patient in the deprescribing decision-making process also serves to improve patient–provider trust and communication.

Thus far, the most effective interventions have focused on patients as the target of the intervention, but work is needed to develop more effective approaches that also integrate changes at the health care provider and health care system level to improve adherence [15]. Some evidence has shown efficacy from large-scale health system and health policy interventions that improve access to medications, but these have yet to be widely tested [16].

In general, interventions have been found to be more effective when using behavioral approaches, rather than cognitive/educational approaches [1, 8]. Interventions delivered directly to patients, preferably using a face-to-face approach, rather than computerized or postal/mail interventions, tend to be more effective [1]. Interventions have been less successful when delivered to health care providers in the hopes that the health care provider will then work to improve patients' medication adherence [1, 17].

Conclusions

Many medication adherence interventions have been tested, but intervention efficacy is highly variable, and has even been shown to be related to the measurement method used, further complicating comparisons across intervention studies [1]. While standardized interventions are more cost-effective to deliver and have been more effective in large trials, interventions will often need to be tailored to the individual needs of the patient to achieve the best results [1, 4]. When developing an intervention program or working with individual patients in clinical practice, it is important to (1) assess each patient's needs and reasons for nonadherence, (2) deliver intervention components designed to meet the patient's needs, (3) evaluate for the impact of the intervention and adjust the intervention

approach as needed, and (4) include some type of long-term maintenance or support to ensure the behavior change persists long term. One consistent feature of adherence interventions is that when interventions are effective, the benefit fades over time if the intervention is not one that continues to support improved adherence over the long term [1, 4].

References

1. Conn VS, Ruppar TM. Medication adherence outcomes of 771 intervention trials: systematic review and meta-analysis. Prev Med. 2017;99:269–76.
2. Peterson AM, Takiya L, Finley R. Meta-analysis of trials of interventions to improve medication adherence. Am J Health Syst Pharm. 2003;60(7):657–65.
3. Roter DL, Hall JA, Merisca R, Nordstrom B, Cretin D, Svarstad B. Effectiveness of interventions to improve patient compliance: a meta-analysis. Med Care. 1998;36(8):1138–61.
4. Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, et al. Interventions for enhancing medication adherence. Cochrane Database Syst Rev. 2014;(11):Cd000011.
5. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol. 2012;73(5):691–705.
6. Conn VS, Ruppar TM, Chan KC, Dunbar-Jacob J, Pepper GA, De Geest S. Packaging interventions to increase medication adherence: systematic review and meta-analysis. Curr Med Res Opin. 2015;31(1):145–60.
7. Choudhry NK, Krumme AA, Ercole PM, Girdish C, Tong AY, Khan NF, et al. Effect of reminder devices on medication adherence: the REMIND randomized clinical trial. JAMA Intern Med. 2017;177(5):624–31.
8. Conn VS, Hafdahl AR, Cooper PS, Ruppar TM, Mehr DR, Russell CL. Interventions to improve medication adherence among older adults: meta-analysis of adherence outcomes among randomized controlled trials. The Gerontologist. 2009;49(4):447–62.
9. Russell CL, Ruppar TM, Matteson M. Improving medication adherence: moving from intention and motivation to a personal systems approach. Nurs Clin North Am. 2011;46(3):271–81.
10. Neiman AB, Ruppar T, Ho M, Garber L, Weidle PJ, Hong Y, et al. CDC grand rounds: improving medication adherence for chronic disease management—innovations and opportunities. MMWR Morb Mortal Wkly Rep. 2017;66(45):1248–51.
11. Abughosh S, Wang X, Serna O, Esse T, Mann A, Masilamani S, et al. A motivational interviewing intervention by pharmacy students to improve medication adherence. J Manag Care Spec Pharm. 2017;23(5):549–60.
12. Dobbels F, De Bleser L, Berben L, Kristanto P, Dupont L, Nevens F, et al. Efficacy of a medication adherence enhancing intervention in transplantation: the MAESTRO-Tx trial. J Heart Lung Transplant. 2017;36(5):499–508.
13. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther. 2001;23(8):1296–310.
14. Reeve E, Wiese MD. Benefits of deprescribing on patients' adherence to medications. Int J Clin Pharm. 2014;36(1):26–9.
15. Berben L, Dobbels F, Engberg S, Hill MN, De Geest S. An ecological perspective on medication adherence. West J Nurs Res. 2012;34(5):635–53.
16. Choudhry NK, Bykov K, Shrank WH, Toscano M, Rawlins WS, Reisman L, et al. Eliminating medication copayments reduces disparities in cardiovascular care. Health Aff (Project Hope). 2014;33(5):863–70.
17. Ruppar TM, Delgado JM, Temple J. Medication adherence interventions for heart failure patients: a meta-analysis. Eur J Cardiovasc Nurs. 2015;14(5):395–404.

Use of Fixed-Dose Combinations in Hypertension and Cardiovascular Disease Prevention

17

Massimo Volpe, Giuliano Tocci, and Giovanna Gallo

17.1 Introduction

Essential hypertension is a clinical condition characterized by high blood pressure (BP) levels and increased risk of developing major cardiovascular diseases, mostly including coronary artery disease, acute myocardial infarction, stroke, renal disease, congestive heart failure and cardiovascular death. For these reasons and considering the persistently high prevalence and growing incidence of hypertension not only in the so-called high-income, but also in the low-income countries, preventive strategies for lowering BP level and achieving effective BP control represent key aspects of healthcare policies [1]. It is well established, in fact, that effective and sustained BP reductions reduce the incidence of hypertension-related complications, independently by age, gender and individual global CV profile [2–4].

Despite the favourable effects provided by lowering BP levels to the recommended targets [5], observational studies and epidemiological surveys have shown unacceptably lower rates of BP control, worldwide [6–8]. Although some recent studies provided more favourable trends in hypertension management and control in various European Countries [9, 10], the global rates of hypertension control remained dramatically poor [11, 12].

M. Volpe, M.D., F.A.H.A., F.E.S.C. (✉) · G. Tocci, M.D., Ph.D.
Division of Cardiology, Department of Clinical and Molecular Medicine, Faculty of Medicine and Psychology, University of Rome Sapienza, Sant'Andrea Hospital, Rome, Italy

IRCCS Neuromed, Pozzilli (IS), Italy
e-mail: massimo.volpe@uniroma1.it

G. Gallo, M.D.
Division of Cardiology, Department of Clinical and Molecular Medicine, Faculty of Medicine and Psychology, University of Rome Sapienza, Sant'Andrea Hospital, Rome, Italy

M. Burnier (ed.), *Drug Adherence in Hypertension and Cardiovascular Protection*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-76593-8_17

Various factors can be advocated for explaining the relatively low rates of BP control observed in the last decades. These include poor patients' adherence to prescribed medications, insufficient physician–patient communication, clinical inertia, availability of heterogeneous sets of guidelines giving often contradictory recommendations on BP targets as well as on therapeutic indications, and excessive pill burden [13, 14]. In particular, a major drive responsible for a substantial proportion of the failure in reaching the recommended BP goals may be linked to the persistently high use of monotherapy in the setting of clinical practice, whereas combination therapy is still largely viewed as a second-choice option for hypertension management [15].

It has been observed that monotherapy can provide effective BP control about one-third of treated hypertensive patients [16, 17], whilst combination strategies with two or three antihypertensive drugs have demonstrated to be very effective in lowering systolic/diastolic BP levels and achieving the recommended BP targets in higher proportions of patients than those obtained with different monotherapies (also when used at full dose) [18]. It is estimated that triple combination therapy is needed in at least 25% of all patients with hypertension in order to control BP [19]. Nonetheless, current North American and European guidelines for the management of arterial hypertension state that two or more drugs are needed in the majority of patients to achieve BP control. In patients with moderate or severe hypertension (Europe) [20] or in those whom BP is 20/10 mmHg above the recommended goal (United States) [21], combining agents from two different drug classes is recommended as the first treatment step. The greater success obtained with combination therapy in hypertensive patients may represent a key factor in motivating patients and physicians, thus improving adherence to treatment, especially when also side effects linked to the high dosages of monotherapies are reduced.

Although different rational combinations of antihypertensive drug classes are currently recommended [20], individual differences and specific advantages have been linked to some therapies as opposed to others. Indeed, not all therapies share the same efficacy and safety profile. For instance, combination therapies of beta-blockers and diuretics or those based on two agents blocking the Renin-Angiotensin System (RAS) are not encouraged by recent recommendations of European guidelines [20]. In contrast, combination therapies based on RAS inhibiting drugs, including angiotensin-converting enzyme (ACE) inhibitors and Angiotensin II receptor blockers (ARBs) with thiazide diuretics [including either hydrochlorothiazide (HCTZ) or indapamide], or calcium channel blockers (CCB), which are characterized by low rates of drug-related side effects and discontinuations, are currently recommended [20].

In this chapter, we will discuss potential advantages of using fixed-dose combination therapies based on RAS inhibiting drugs and either thiazide diuretics or CCBs, or both, to improve BP control and achieve higher adherence to antihypertensive drug therapies. These specific combinations are strongly advocated by international guidelines and have been well documented in several large randomized clinical trials.

17.2 Antihypertensive Drug Classes to Be Used in Combination Therapy

Current hypertension guidelines support the use of five classes of antihypertensive drugs for the initial choice in hypertensive patients at low-to-moderate global cardiovascular risk factor or in those with grade 1 hypertension [20]. In the presence of high or very high cardiovascular risk profile, grade 2–3 hypertension or after demonstrating inefficacy of monotherapy at adequate dosage, combination therapy can be used for lowering BP levels and achieving BP control [20]. In view of the fact that the vast majority of treated hypertensive patients require a combination therapy for reducing BP levels to the recommended targets, so that the choice of the initial drug has been often considered not clinically relevant.

It should be noted, however, that if by one side all the recommended drug classes have demonstrated to be effective and safe in lowering BP levels and reducing incidence of major cardiovascular complications, from the other side they do not share the same safety and tolerability profiles. Several observational studies have reported higher rates of discontinuations with beta-blockers and diuretics compared to CCBs, ACE inhibitors and ARBs [22, 23]. Discontinuations from prescribed antihypertensive therapy can be due to lack of BP lowering efficacy and occurrence of drug-related side effects, and hypertensive patients who discontinued antihypertensive medications remain at high risk of cardiovascular and cerebrovascular complications. For these reasons, it would be useful to adopt antihypertensive drug therapy including either ACE inhibitors or ARBs for ameliorating hypertension management and control.

Indeed, the benefits of RAS inhibiting drugs have been demonstrated in different clinical settings throughout the whole cardiovascular continuum, from asymptomatic patients with high BP to refractory congestive heart failure [24]. In particular, the favourable effects of RAS blocking agents have been extensively and independently tested in large, representative, randomized, controlled clinical trials, which consistently demonstrated that these drugs reduce CV morbidity and mortality without differences between ACE inhibitors and ARBs in terms of major cardiovascular outcomes [25]. More recently, the substantial equivalence between these two classes in terms of protection from major CV events (i.e. myocardial infarction, stroke, heart failure and cardiovascular death) has been also confirmed by the ONgoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) [26]. It should be also noted, however, that in the same trial, combination therapy based on ACE inhibitors plus ARBs did not provide any additional advantages in terms of BP reductions or CV protection; yet, such approach was affected by higher rates of drug discontinuations due to drug-related side effects and adverse reactions (mostly including symptomatic hypotension and impaired renal function with hyperkalaemia) compared to either monotherapies [26].

On the basis of these findings from the ONTARGET [26] and other randomized clinical trials that directly tested combination therapies based on ACE inhibitors plus ARBs versus either monotherapies [27–29], and reported high rates of adverse events without additional benefits in terms of reduced BP levels, this combination

therapy is currently not recommended for the clinical management of hypertension. Similar recommendation has been also set for combination therapy based on direct renin inhibitor (aliskiren) plus ACE inhibitors or ARBs or both, due to deterioration of renal function and electrolytes imbalance reported in diabetic patients at high CV risk profile [30, 31].

On the other hand, both ACE inhibitors and ARBs have been safely and effectively associated with other classes of antihypertensive drugs, mostly including CCBs or diuretics, for lowering BP levels and achieving the recommended BP targets. Such combination therapies have also demonstrated to be safe and well-tolerated in various clinical settings. For example, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), about 30% of patients allocated in all treatment arms was on combination therapy at 6 months after the beginning of the study with more than 65% at the end of the study; the proportions of treated controlled hypertensive patients in this trial raised from 30–60%, accordingly [32, 33]. In the Losartan Intervention For End-point reduction in hypertension (LIFE) trial [34], about 70% of patients allocated in both treatment arms was on combination therapy at 6 months after the beginning of the study with more than 85% at the end of the study. Also in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) trial [35], most patients (78%) were taking at least two antihypertensive agents, and only 15% and 9% were taking amlodipine and atenolol monotherapy, respectively. More recently, in the Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial [36], the use of combination therapy from the beginning of the study resulted in a very high percentage (about 80%) of patients with controlled BP levels at the end of the trial (Fig. 17.1). Even in this trial, antihypertensive therapy based on ACE inhibitor plus CCB

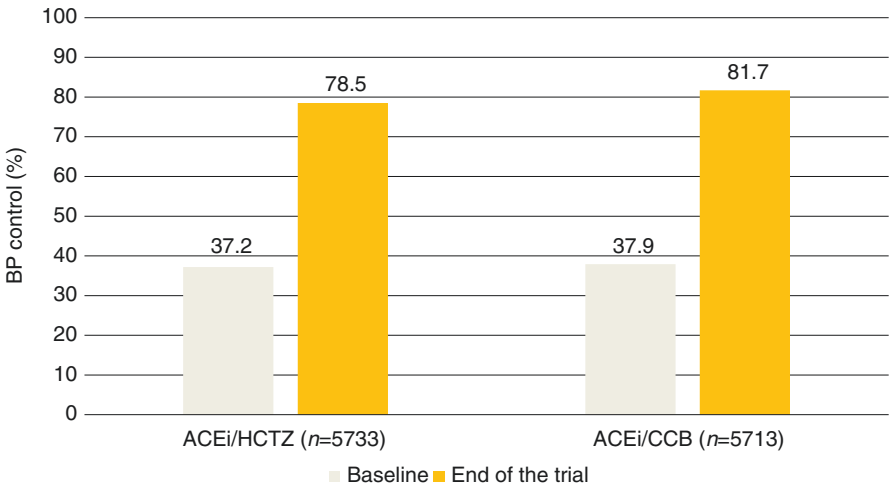


Fig. 17.1 Proportions of patients achieving the recommended blood pressure targets at the beginning and at the end of the ACCOMPLISH trial. Derived from [36]

resulted in significantly lower incidence of major CV events than that of ACE inhibitor plus diuretic [36]. Based on these findings, it has been suggested that implementing the use of combination strategies based on drugs able to inhibit the deleterious effects of abnormal RAS activation in the clinical management of hypertension may also improve BP control and tolerability, beyond the favourable effects on cardiovascular protection.

The rationale of combination therapy based on RAS blockers in hypertension should be related not only to an increased BP lowering efficacy due to the synergistic and additive effects on BP reduction provided by different compounds [37–39]. In addition, it may be linked to the favourable impact on several pathophysiological mechanisms of hypertension, as well as to the inhibition of the contra-regulatory mechanisms, thus leading to a reduced incidence of drug-related side effects and hence improved tolerability [37–39]. In addition, these combination strategies can be effectively and safely applied in most hypertension-related clinical conditions [40, 41].

Nowadays, combination therapies based on RAS blocking agents appear to be rational for a number of pharmacological, therapeutic and clinical reasons. First, these strategies are based on the concomitant use of the most documented antihypertensive agents, which, together, usually show better results on BP control. Secondly, they are substantially neutral or favourable on metabolism (i.e. reduced incidence of new-onset diabetes mellitus), when compared with traditional combination therapy. Finally, they have important clinical advantages in terms of tolerability, by providing a significant reduction of side effects because of antagonistic cross actions of RAS blocking agents on other agents present in the combination and because of the usually minor dosage required of each active component. For instance, combining a RAS blocker with a CCB improves the tolerability profile of the latter by reducing the incidence of peripheral oedema and also blunting the heart rate acceleration occasionally observed with a dihydropyridine CCB [19].

17.3 Antihypertensive Drug Classes and Adherence to Therapy

Low adherence is the most common cause of difficult to treat true or apparent resistant hypertension [42]. In addition, poor adherence to prescribed antihypertensive medications has been associated to increased risks of cardiovascular and cerebrovascular events, which further increase the burden of hypertension-related disease [43].

In view of the persistently low rates of BP control and the increasing prevalence of poor adherence to antihypertensive drug therapies, European Society of Hypertension (ESH)/European Society of Cardiology (ESC) guidelines provide recommendations on methods to improve adherence to physicians' recommendations, and adherence management is also becoming part of care pathways [44–46].

Drug adherence problems are characterized by two major patterns: (1) non-persistence on therapy; (2) good persistence but poor implementation of the dosing

regimen (primarily missed doses and drug holidays). Identification of the problem is a crucial aspect, since the prevention strategy depends on the type of pattern. Persistence is more problematic than daily implementation in hypertension, given the long-term nature of the condition [47].

In addition to determining whether drugs are taken, it is important to assess drug adherence. The difficulty of accurately assessing adherence is highlighted by a study by Meddings et al. [48], where primary care providers recognized non-adherence for less than half of those patients who had significant gaps in their refill history. Apps are a conceptual way to implement adherence; however, there are too many, they work for a limited time, are often generic and even if they provide feedback to the healthcare provider they are too complicated.

There are several non-invasive and invasive methods of measuring adherence. There is no one gold standard method of measuring adherence; a combination of methods should be used to measure initiation, implementation and persistence which should be individualized. The most accurate methods are electronic monitoring and drug or biomarker measurement. Electronic monitors are pill containers that record the date and time when opened, and may be useful in the management of patients with resistant hypertension [49]. Although not available in all countries, they are recognized as an underutilized resource. They have the advantage of being a dynamic measure, but do not prove ingestion. Monitoring of drug levels has been shown to improve blood pressure control at follow-up visits [50]. Whilst blood or urine drug measurements prove ingestion they are invasive and costly. The Medication Event Monitoring System (MEMS) is an example of an electronic medication monitoring, measurement and adherence system. The limitations of using blood or urine measurements to monitor adherence, compared with the MEMS, are illustrated by the cases of three patients, who all had blood levels in the therapeutic range despite a considerable variation in the number of dosing events during the days before the drug levels were measured. Furthermore, monitoring of two different drug treatments for 1 year in three patients showed a difference in adherence between treatments. A meta-analysis of the impact of different strategies to improve adherence and blood pressure control demonstrated that collaboration with healthcare partners has the greatest impact.

Other systems in development for monitoring adherence include ingestible sensor systems combined with wireless observed therapy [51] and electronically chipped packaging. It is anticipated that in the future, adherence monitoring will become routine for chronic conditions at specific time points, i.e. initiation and treatment failure.

17.4 Strategies to Improve Adherence

A number of different strategies can be used to improve BP control [52, 53]. As previously discussed, the vast majority of patients need combination therapy to achieve the recommended BP targets, since excessive pill burden is associated with lower adherence [54]. Dosing frequency is also an important aspect and may promote

non-persistence, in cases of frequent dosing of prescribed medications. For these reasons, treatment simplification is one of the most straightforward ways to enhance adherence, by facilitating implementation of the dosing regimen [55, 56]. Single-pill fixed-dose combination therapies can reduce pill burden and simplify treatment regimens [44], and improve adherence and improve BP normalization ratios compared with free combinations [57, 58]. Efforts to take advantage of the benefits of fixed-dose combination therapies for improving adherence include an angiotensin-receptor-blocker-based hypertension treatment platform. This is a practical tool which has been devised to guide the use of single-pill FDCs containing two- and even three drugs in clinical situations commonly seen in hypertension [59].

Patients' awareness of their adherence patterns can change their behaviour [60]. The key elements to changing patients' behaviour include: education, motivation and measurement of adherence [61]. Packaging has a major role in education and measurement. The ESH/ESC guidelines include reminder packaging as a method of improving adherence to physicians' recommendations [44]. A real-world assessment of the impact of reminder packaging in the USA has shown that it can improve adherence and persistence rates to antihypertensive treatment [62]. This approach to improving adherence through improvements in packaging is now being applied within Europe.

Repacking products in this way should be considered as a major step in improving initiation, supporting implementation and ultimately persistence to treatment. Other important considerations to engage discussion between patients and healthcare providers are: materials to support counselling; dummy packaging. It is recognized that pharmaceutical manufacturers could do more with regard to improving packaging of medications; small changes may have a meaningful impact on adherence.

Conclusions

The benefits obtained by achieving effective and persistent BP control in hypertensive patients with different CV risk profile in terms of reduction of CV morbidity and mortality have been repeatedly demonstrated. Despite these solid evidence, large international surveys still document persistently low rates of BP control in the general hypertensive population. The relatively low use of combination therapy and the lack of drug dosage optimization during chronic antihypertensive treatment represent two of the plausible reasons for this paradox. Another crucial aspect is represented by low adherence to prescribed medications, mostly due to the occurrence of drug-related side effects and adverse reactions, which may induce drug discontinuations and interruptions during chronic antihypertensive therapy.

Combination therapies based on RAS blocking agents have demonstrated to significantly contribute to improve BP control in the presence of an excellent tolerability profile, especially when used in fixed-dose combination therapies (single-pill approach). Moreover, the use of single-pill combination is no longer hampered by the loss of dosing flexibility, being available a choice of different doses of each component, therefore allowing the clinician to build up a personalized and simplified anti-hypertensive therapy with just one pill.

References

1. Tocci G, Sciarretta S, Facciolo C, Volpe M. Antihypertensive strategy based on angiotensin II receptor blockers: a new gateway to reduce risk in hypertension. Expert Rev Cardiovasc Ther. 2007;5(4):767–76.
2. Turnbull F, Neal B, Algert C, Chalmers J, Chapman N, Cutler J, et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. Arch Intern Med. 2005;165(12):1410–9.
3. Turnbull F. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials. Lancet. 2003;362(9395):1527–35.
4. Turnbull F, Neal B, Ninomiya T, Algert C, Arima H, Barzi F, et al. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. BMJ. 2008;336(7653):1121–3.
5. Williams B. The year in hypertension. J Am Coll Cardiol. 2009;55(1):65–73.
6. Kotseva K, Wood D, De Backer G, De Bacquer D, Pyorala K, Keil U. Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries. Lancet. 2009;373(9667):929–40.
7. Whyte JL, Lapuerta P, L'Italien GJ, Franklin SS. The challenge of controlling systolic blood pressure: data from the National Health and Nutrition Examination Survey (NHANES III), 1988--1994. J Clin Hypertens (Greenwich). 2001;3(4):211–6.
8. Wolf-Maier K, Cooper RS, Kramer H, Banegas JR, Giampaoli S, Joffres MR, et al. Hypertension treatment and control in five European countries, Canada, and the United States. Hypertension. 2004;43(1):10–7.
9. Tocci G, Nati G, Cricelli C, Parretti D, Lapi F, Ferrucci A, et al. Prevalence and control of hypertension in the general practice in Italy: updated analysis of a large database. J Hum Hypertens. 2017;31(4):258–62.
10. Tocci G, Muiesan ML, Parati G, Agabiti Rosei E, Ferri C, Virdis A, et al. Trends in prevalence, awareness, treatment, and control of blood pressure recorded from 2004 to 2014 during world hypertension day in Italy. J Clin Hypertens (Greenwich). 2016;18(6):551–6.
11. Ezzati M, Oza S, Danaei G, Murray CJ. Trends and cardiovascular mortality effects of state-level blood pressure and uncontrolled hypertension in the United States. Circulation. 2008;117(7):905–14.
12. Danaei G, Finucane MM, Lin JK, Singh GM, Paciorek CJ, Cowan MJ, et al. National, regional, and global trends in systolic blood pressure since 1980: systematic analysis of health examination surveys and epidemiological studies with 786 country-years and 5.4 million participants. Lancet. 2011;377(9765):568–77.
13. Bramlage P, Bohm M, Volpe M, Khan BV, Paar WD, Tebbe U, et al. A global perspective on blood pressure treatment and control in a referred cohort of hypertensive patients. J Clin Hypertens (Greenwich). 2010;12(9):666–77.
14. Volpe M, Tocci G. Challenging hypertension: how to diagnose and treat resistant hypertension in daily clinical practice. Expert Rev Cardiovasc Ther. 2010;8(6):811–20.
15. Tocci G, Giovannelli F, Sciarretta S, Ferrucci A, Zito GB, Volpe M. Management of hypertension and stroke prevention: results of the Italian cardiologist survey. Int J Clin Pract. 2009;63(2):207–16.
16. Chrysant SG. Fixed combination therapy of hypertension: focus on valsartan/hydrochlorothiazide combination (Diovan/HCT). Expert Rev Cardiovasc Ther. 2003;1(3):335–43.
17. Tocci G, Palano F, Pagannone E, Chin D, Ferrucci A, Volpe M. Fixed-combination therapies in hypertension management: focus on enalapril/lercanidipine. Expert Rev Cardiovasc Ther. 2009;7(2):115–23.
18. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 ESH-ESC practice guidelines for the management of arterial hypertension: ESH-ESC task force on the management of arterial hypertension. J Hypertens. 2007;25(9):1751–62.

19. Gradman AH. Rationale for triple-combination therapy for management of high blood pressure. J Clin Hypertens (Greenwich). 2010;12(11):869–78.
20. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2013;31(7):1281–357.
21. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311(5):507–20.
22. Corrao G, Parodi A, Zambon A, Heiman F, Filippi A, Cricelli C, et al. Reduced discontinuation of antihypertensive treatment by two-drug combination as first step. Evidence from daily life practice. J Hypertens. 2010;28(7):1584–90.
23. Corrao G, Zambon A, Parodi A, Poluzzi E, Baldi I, Merlino L, et al. Discontinuation of and changes in drug therapy for hypertension among newly-treated patients: a population-based study in Italy. J Hypertens. 2008;26(4):819–24.
24. Volpe M, Tocci G, Pagannone E. Fewer mega-trials and more clinically oriented studies in hypertension research? The case of blocking the renin-angiotensin-aldosterone system. J Am Soc Nephrol. 2006;17(4 Suppl 2):S36–43.
25. Turnbull F, Neal B, Pfeffer M, Kostis J, Algert C, Woodward M, et al. Blood pressure-dependent and independent effects of agents that inhibit the renin-angiotensin system. J Hypertens. 2007;25(5):951–8.
26. Investigators O, Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med. 2008;358(15):1547–59.
27. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet. 2003;362(9386):767–71.
28. Dickstein K, Kjekshus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. Optimal Trial in Myocardial Infarction with Angiotensin II Antagonist Losartan. Lancet. 2002;360(9335):752–60.
29. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau JL, Kober L, Maggioni AP, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. N Engl J Med. 2003;349(20):1893–906.
30. Parving HH, Brenner BM, McMurray JJ, de Zeeuw D, Haffner SM, Solomon SD, et al. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N Engl J Med. 2012;367(23):2204–13.
31. Parving HH, Persson F, Lewis JB, Lewis EJ, Hollenberg NK. Aliskiren combined with losartan in type 2 diabetes and nephropathy. N Engl J Med. 2008;358(23):2433–46.
32. Cushman WC, Ford CE, Cutler JA, Margolis KL, Davis BR, Grimm RH, et al. Success and predictors of blood pressure control in diverse North American settings: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). J Clin Hypertens (Greenwich). 2002;4(6):393–404.
33. Cushman WC, Ford CE, Einhorn PT, Wright JT Jr, Preston RA, Davis BR, et al. Blood pressure control by drug group in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). J Clin Hypertens (Greenwich). 2008;10(10):751–60.
34. Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, de Faire U, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet. 2002;359(9311):995–1003.
35. Dahlof B, Sever PS, Poulter NR, Wedel H, Beevers DG, Caulfield M, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. Lancet. 2005;366(9489):895–906.

36. Jamerson K, Weber MA, Bakris GL, Dahlof B, Pitt B, Shi V, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. N Engl J Med. 2008;359(23):2417–28.
37. Messerli FH, Michalewicz L. Cardiac effects of combination therapy. Am J Hypertens. 1997;10(7 Pt 2):146S–52S.
38. Messerli FH, Grossman E, Michalewicz L. Combination therapy and target organ protection in hypertension and diabetes mellitus. Am J Hypertens. 1997;10(9 Pt 2):198S–201S.
39. Messerli FH. Combination therapy in hypertension. J Hum Hypertens. 1992;6(Suppl 2):S19–21.
40. Bangalore S, Shahane A, Parkar S, Messerli FH. Compliance and fixed-dose combination therapy. Curr Hypertens Rep. 2007;9(3):184–9.
41. Ruschitzka FT, Noll G, Luscher TF. Combination of ACE inhibitors and calcium antagonists: a logical approach. J Cardiovasc Pharmacol. 1998;31(Suppl 2):S5–16.
42. Jung O, Gechter JL, Wunder C, Paulke A, Bartel C, Geiger H, et al. Resistant hypertension? Assessment of adherence by toxicological urine analysis. J Hypertens. 2013;31(4):766–74.
43. Corrao G, Parodi A, Nicotra F, Zambon A, Merlino L, Cesana G, et al. Better compliance to antihypertensive medications reduces cardiovascular risk. J Hypertens. 2011;29(3):610–8.
44. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34(28):2159–219.
45. Heidbuchel H, Verhamme P, Alings M, Antz M, Diener HC, Hacke W, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. Europace. 2015;17(10):1467–507.
46. PriceWaterhouseCoopers. Pharma 2020: supplying the future. Which path will you take? 2007 [cited 2016 15 September]. https://www.pwc.com/gx/en/pharma-life-sciences/pdf/pharma-2020-supplying-the-future.pdf.
47. Blaschke TF, Osterberg L, Vrijens B, Urquhart J. Adherence to medications: insights arising from studies on the unreliable link between prescribed and actual drug dosing histories. Annu Rev Pharmacol Toxicol. 2012;52:275–301.
48. Meddings J, Kerr EA, Heisler M, Hofer TP. Physician assessments of medication adherence and decisions to intensify medications for patients with uncontrolled blood pressure: still no better than a coin toss. BMC Health Serv Res. 2012;12:270.
49. Burnier M, Schneider MP, Chiolero A, Stubi CL, Brunner HR. Electronic compliance monitoring in resistant hypertension: the basis for rational therapeutic decisions. J Hypertens. 2001;19(2):335–41.
50. Brinker S, Pandey A, Ayers C, Price A, Raheja P, Arbique D, et al. Therapeutic drug monitoring facilitates blood pressure control in resistant hypertension. J Am Coll Cardiol. 2014;63(8):834–5.
51. Belknap R, Weis S, Brookens A, Au-Yeung KY, Moon G, DiCarlo L, et al. Feasibility of an ingestible sensor-based system for monitoring adherence to tuberculosis therapy. PLoS One. 2013;8(1):e53373.
52. Volpe M, Ambrosioni E, Borghi C, Cottone S, Cuspidi C, De Luca N, et al. Strategies for improving blood pressure control in Italy: from global cardiovascular risk stratification to combination therapy. 2012 Position paper of the Italian Society of Hypertension. G Ital Cardiol. 2012;13(12):853–60.
53. Volpe M, Rosei EA, Ambrosioni E, Cottone S, Cuspidi C, Borghi C, et al. 2012 consensus document of the Italian Society of Hypertension (SIIA): strategies to improve blood pressure control in Italy: from global cardiovascular risk stratification to combination therapy. High Blood Press Cardiovasc Prev. 2013;20(1):45–52.
54. Gerbino PP, Shoheiber O. Adherence patterns among patients treated with fixed-dose combination versus separate antihypertensive agents. Am J Health Syst Pharm. 2007;64(12):1279–83.
55. Burnier M, Brown RE, Ong SH, Keskinaslan A, Khan ZM. Issues in blood pressure control and the potential role of single-pill combination therapies. Int J Clin Pract. 2009;63(5):790–8.

56. Redon J, Brunner HR, Ferri C, Hilgers KF, Kolloch R, van Montfrans G. Practical solutions to the challenges of uncontrolled hypertension: a white paper. J Hypertens Suppl. 2008;26(4):S1–14.
57. Sherrill B, Halpern M, Khan S, Zhang J, Panjabi S. Single-pill vs free-equivalent combination therapies for hypertension: a meta-analysis of health care costs and adherence. J Clin Hypertens. 2011;13(12):898–909.
58. Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis. Hypertension. 2010;55(2):399–407.
59. Volpe M, de la Sierra A, Kreutz R, Laurent S, Manolis AJ. ARB-based single-pill platform to guide a practical therapeutic approach to hypertensive patients. High Blood Press Cardiovasc Prev. 2014;21(2):137–47.
60. Vrijens B, Belmans A, Matthys K, de Klerk E, Lesaffre E. Effect of intervention through a pharmaceutical care program on patient adherence with prescribed once-daily atorvastatin. Pharmacoepidemiol Drug Saf. 2006;15(2):115–21.
61. Vrijens B, Urquhart J, White D. Electronically monitored dosing histories can be used to develop a medication-taking habit and manage patient adherence. Expert Rev Clin Pharmacol. 2014;7(5):633–44.
62. Dupclay L, Eaddy M, Jackson J, Raju A, Shim A. Real-world impact of reminder packaging on antihypertensive treatment adherence and persistence. Patient Prefer Adherence. 2012;6:499–507.

Nurse Led Interventions in Hypertension

18

Christopher E. Clark

18.1 Introduction

Raised blood pressure is the main risk factor globally for premature morbidity and mortality [1]. Globally it affected close to one billion adults (26% of the population) in 2000, and is projected to rise to 1.6 billion by 2025 [2]. This makes measurement of blood pressure a common reason for consultation in primary care [3], and rising workload and availability of doctors in primary care is an international concern [4, 5]. In English primary care consultation rates for general practitioners rose by 13.6% over the 7 years to 2014, whilst rates for nurses rose by only 0.9% during the same period [6]. It is suggested that transfer of some clinical roles from doctors to nurses may help to alleviate the growing workforce crisis, and reviews suggest that appropriately trained nurses can deliver care with the same quality and outcomes as doctors [7].

A 10 mmHg reduction in systolic blood pressure is estimated to achieve a 41% reduction in stroke and a 22% reduction in coronary heart disease [8]. Whilst blood pressure control is improving over time, the detection and adequate management of high blood pressure remains a challenge [9]. Nurse led care in hypertension is seen as one means of improving implementation of guidelines on blood pressure management [10, 11]. Resource limitations also encourage substitution of doctors by nurses and other allied health professionals in the belief that they are less costly [12]; however, it continues to be noted that the evidence for this is too limited to support such conclusions [13].

C. E. Clark
Primary Care Research Group, University of Exeter Medical School, Smeall Building, St Luke's Campus, Exeter, UK

Institute of Health Services Research, Exeter, UK
e-mail: c.e.clark@exeter.ac.uk

M. Burnier (ed.), *Drug Adherence in Hypertension and Cardiovascular Protection*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-76593-8_18

18.2 Nurse Substitution in Hypertension

Trials of nurse led care have been appearing since the 1990s [14–16]; however, Oakeshott concluded in her 2003 systematic review that there was a lack of robust evidence of effectiveness for nurse led care in hypertension. The 2010 Cochrane update by Glynn et al. found evidence of greater reduction of blood pressure with nurse led care but concluded that it required further evaluation [17], whilst our own focussed systematic review in the same year found some evidence to suggest that outcomes were improved when nurse prescribers were involved in some health care settings. We concluded, however, that there was insufficient evidence to support widespread deployment of nurses in the management of hypertension [18].

In practice, there has been shift in hypertension care over the last decade from doctors to nurses and health care assistants, and rising numbers of nurse prescribers are becoming active in hypertension [19]. A multidisciplinary approach can improve control in resistant hypertension, and nurses record lower blood pressures than doctors due to smaller white coat effects [20–22], thus there seem good reasons to involve nurses in hypertension care. In 2003, Bengtson and Drevenhorn examined and identified the roles of nurses in hypertension care (Box 18.1) [23]. In their review, they called for further well-designed studies to develop nursing care for hypertension, and over 50 randomised controlled trials have been published during the last 15 years. Within our current systematic review of allied health professional led care in hypertension, we have reviewed evidence from randomised controlled trials that compare nurse led care with usual care (defined as doctor led care) [24]. These are considered with relevant pooled findings in the following sections.

Box 18.1 Roles of the Nurse in Hypertension Care; After Bengtson and Drevenhorn 2003 [23]

- Team member or team leader
- Measurement of blood pressure—avoiding white coat effect
- Educator in non-pharmacological treatment
- Translator for the physician with a holistic and psychosocial approach
- Promoting lifestyle changes
- Promoting medication adherence
- Titrating blood pressure treatment to target
- Monitoring and maintaining blood pressure treatment

18.2.1 Settings for and Subjects of Interventions

Hypertension is largely diagnosed and managed in primary care, and general or family practice settings have been the usual locations for studies of nurse led interventions [15, 25–47]. Trials have examined nurse led care in a variety of other settings, with evidence from individual randomised controlled trials for lower outcome blood pressures following delivery at home [48–53], in community

centres [48, 54–56], faith groups [57], community walking groups [58], and in secondary care clinics for hypertension [59], diabetes [60–63], cardiology [64, 65], stroke [66], or general medicine [67, 68]. Greater achievement of study blood pressure targets has also been demonstrated in workplace based interventions [14, 69, 70]. Target achievement is less often improved within individual trials but pooled analyses confirm evidence of benefit from community settings (Odds Ratio (OR) for target achievement with intervention 1.9 (95%CI 1.2–3.0); 7 studies, 2820 participants) [14, 51, 70–74], primary care settings (OR 1.4 (1.1–1.6); 13 studies, 11,278 participants) [15, 25, 26, 29, 34, 35, 38, 41, 45, 47, 65, 75, 76], and secondary care settings (OR 1.8 (1.3–2.5); 11 studies, 3605 participants) [32, 36, 59–61, 63, 64, 66, 67, 77, 78].

Studies have found evidence of benefit for nurse led interventions from around the globe, thereby including a range of different ethnic populations. Culturally appropriate health education may improve outcomes in ethnic minorities [79], so some trials have specifically targeted ethnic subgroups regarded as underserved within their respective countries. Improved blood pressure lowering has been demonstrated in African-American cohorts [25, 34, 35, 37, 42, 48, 54, 56, 67, 71], American Hispanic people [42, 67], First Nations American Indian people [49], Maoris [80], and South Asians [75, 81]. A substantial number of trials have focussed on control of hypertension with diabetes, suggesting that the findings summarised here can be applied to hypertensives with and without coincident diabetes [17, 27, 28, 32, 37, 38, 49, 59–63, 74–76, 78, 82, 83].

Trials usually seek to recruit subjects with uncontrolled (i.e. above study or protocol target) blood pressures. Only a few studies have restricted recruitment to controlled hypertensives; although some have shown benefit [27, 61], they are outweighed by those that fail to show improved blood pressure outcomes [34, 61, 82]. Therefore the evidence summarised in this chapter should be viewed as relevant to populations with uncontrolled hypertension.

18.2.2 Features of Interventions

18.2.2.1 Mode of Review or Follow-Up

Interventions in randomised controlled trials usually include face to face contact with nurses, with or without other modalities. Nurse delivered telephone support for patients, without face to face contact, appears to be ineffective in delivering lower outcome blood pressures compared to usual care [25, 26, 28, 34, 35, 37, 52, 66, 77]. Other trials have used telephone support to supplement face to face reviews [39, 45, 54, 58, 71, 73, 74], but on pooled analysis these show no superiority of systolic blood pressure outcomes compared to interventions based purely on face to face review [27, 29, 30, 32, 33, 36, 44, 49–51, 56, 59, 61, 62, 64, 72, 75, 78, 80, 83–85], whilst mean reduction of diastolic pressures compared to usual care is actually greater for face to face interventions without telephone support than with it (−2.1 mmHg (−3.0 to −1.2); 22 studies, 7793 participants without telephone support vs. −0.9 mmHg (−2.4 to 0.6); 7 studies, 2198 participants; $p = 0.03$). This

pattern is also seen for achievement of study blood pressure targets. These are complex interventions so caution is needed in interpreting these findings; however, it may be that combined interventions, by using telephone consultations as a substitute for face to face interim reviews, reduce the frequency of face to face contact (see below). Whatever the cause we can conclude that the routine use of nurse led telephone support for blood pressure lowering is at least ineffective, and possibly counterproductive.

18.2.2.2 Use of a Management Algorithm

Our previous systematic review in 2010 found that effective nurse led interventions for hypertension require an algorithm to structure care [18]. Taking account of newer studies, differences in trial outcomes are no longer seen between studies using or not using an algorithm to structure care; however, the quality of reporting of study methods varies [86]. The majority of randomised trials of nurse led care do include an algorithm, and it is likely that, where not stated, other trials also had some structured care component. Structured care has emerged from previous reviews as an important component of effective interventions [87, 88]. Where treatment changes are explicit this may help to overcome clinical inertia [89], therefore a treatment algorithm remains an essential basis for nurse led care in hypertension.

18.2.2.3 Adherence/Education/Support

Physicians recognise the importance of addressing medication non-adherence but less often actually do so [90]. Many interventions include an element of education and lifestyle advice [56, 60, 64, 67, 71, 74], or medication adherence support [48]. These elements coupled with regular review are key components of effective long-term care, to which the nurse–patient relationship is central [91]. Education and explanation are key to improving medication adherence [92], which is often found to be higher in clinical trials than in routine care [93]. Education is usually only one element of a complex intervention in trials of nurse led care, so it is not clear from existing trials how important it is that any educational interventions for hypertension are delivered specifically by nurses. Evidence linking medication adherence and blood pressure outcomes is unclear [94]. Existing trials have assessed medication adherence using questionnaires such as the Morisky scale [95], which are only modestly effective in detecting medication non-adherence in comparison to electronic pill box monitoring [96, 97]. Thus specific well-designed studies using a robust method of adherence assessment are needed, to clarify whether nurse led educational interventions can be linked to improved medication adherence and better blood pressure outcomes.

18.2.2.4 Home Monitoring

Self-monitoring of blood pressure alone [98], or with electronic transmission of results to physicians can improve blood pressure control [99, 100], but the effect is enhanced when self-monitoring is combined with additional support to the patient [101]. Interventions including nurse monitoring and feedback on home blood pressure readings have proved effective compared to usual care [48, 53]. Home blood

pressure readings are associated with lower outcome blood pressures and greater achievement of study targets than clinic measurements [102]. It is not clear whether this difference, in relation to nurse led care, can be wholly accounted for by the interventions themselves or may be confounded by differences due to setting and white coat effects [21]: further evidence is required however the recently published TASMINH4 trial has confirmed the benefits of self-monitoring, with or without telemonitoring, when used by general practitioners to titrate antihypertensive medication in individuals with poorly controlled blood pressure [103]. Further work is needed to understand the role of the nurse in receiving, interpreting, and acting upon patient measured blood pressure readings.

18.2.2.5 Prescribing

We have previously found greater reductions in blood pressure where interventions include nurse prescribing compared to continued prescribing by doctors, and documented a rising proportion of nurses prescribing in hypertension in our region over time [18, 19]. A more recent review of studies substituting prescribing by nurses or pharmacists for prescribing by doctors has also reported overall lower outcome blood pressures, although nurse led care was not reported separately [104]. On pooled analysis of randomised controlled trials, there is a trend towards increasingly greater reductions in systolic but not diastolic blood pressure for interventions that include nurse prescribing (difference in change in systolic blood pressure −6.4 mmHg (−9.1 to −3.8); 10 studies, 4285 participants) [32, 49, 53, 59, 60, 67, 71, 74, 78, 105], compared to nurses advising changes to medication (−4.4 mmHg (−6.2 to −2.6); 8 studies, 2522 participants) [25, 29, 51, 56, 61, 73, 77, 82] or no nursing intervention for medication (−3.2 mmHg (−5.3 to −1.2); 32 studies, 9522 participants) [26, 28, 30, 31, 33–37, 39, 40, 44–48, 50, 52, 54, 58, 62, 64, 66, 68, 72, 73, 75, 80, 81, 83–85].

18.2.2.6 Frequency of and Intensity of Intervention

There is marked variation in the frequency of face to face reviews of patients between trials, with greater reductions of systolic blood pressure for interventions that involve at least monthly contact until blood pressure reaches target (systolic reduction −7.2 mmHg (−10.5 to −3.9); 19 studies, 3760 participants) [29, 37, 46, 47, 54, 55, 58, 59, 61, 64, 68, 72, 74, 77, 80, 81, 83, 84] compared to less frequent interventions (−2.8 mmHg (−3.8 to −1.8); 32 studies, 12,523 participants; $p = 0.01$) [25, 26, 28, 30–36, 39, 40, 44–54, 56, 60, 62, 67, 73, 75, 78, 82, 85]. Study blood pressure targets are also more frequently attained, compared to usual care, when interventions are delivered at least monthly (RR 1.5 (1.2–2.0); 12 studies, 2915 participants) [14, 29, 47, 55, 59, 61, 64, 66, 70, 72, 74, 77] compared to less frequently (1.1 (1.0–1.2); 21 studies, 15,011 participants; $p = 0.02$) [15, 25, 26, 32, 34–36, 38, 41, 43, 45, 47, 51, 60, 63, 65, 67, 73, 75, 76, 78].

By taking account of the interaction between the presence or absence of, and the frequency of, face to face to face interventions and the ability to change prescriptions, it is possible to demonstrate a hierarchy of effectiveness for nurse led interventions to lower blood pressure (Fig. 18.1; $p < 0.001$ for subgroup differences).

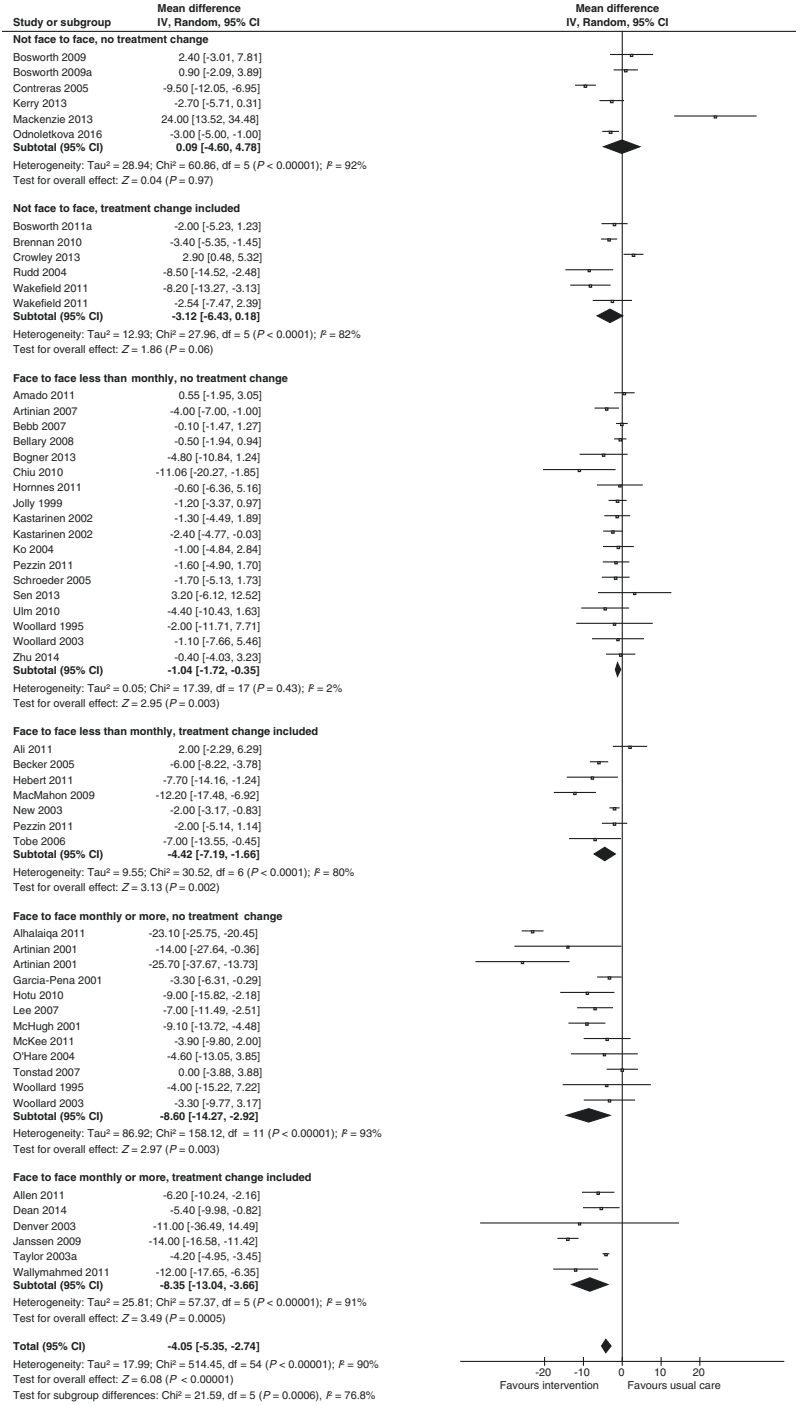


Fig. 18.1 Changes in systolic blood pressure for nurse led interventions compared to usual care grouped by intensity of intervention

Interventions without face to face contact, themselves ineffective on pooled analysis, are enhanced by the ability to alter medications. The same is found for low frequency (less than monthly) face to face interventions; however, greatest differences in blood pressure reductions for nurse led interventions compared to usual care are observed when face to face review occurs at least monthly. Interestingly, at this level of intervention there seems to be no significant additional benefit in altering medications (systolic mean difference −8.6 mmHg (−14.3 to −2.9) without medication change vs. −8.4 mmHg (−13.0 to −3.7) with medication changes; $p = 0.95$ for differences), suggesting that frequent face to face reviews may be the most effective element of these interventions.

We have found that frequent nurse led dose titration to achieve rapid control of blood pressure is both safe and feasible [106]. A recent large retrospective study found that delays of greater than 1.4 months before intensifying treatment towards target were associated with higher risks of cardiovascular event or death over 10 years, hinting at the possibility that intensive interventions to control blood pressure quickly may have longer term benefits for outcomes [107].

18.3 Costs and Cost-Effectiveness of Interventions

Costs of nurse led interventions are infrequently reported as primary outcome measures. Costs will be dependent on the health care system in which the interventions are based; however, data were only identified from trials in the UK [44, 75], USA [35, 55, 73, 77, 108] and one group in Canada [69, 70]. With one exception, a trial of workplace based nurse interventions [69], costs are higher for nurse led care compared to usual (doctor led) care. Excess costs per patient per year ranged from $212 to $1153 per patient per year, representing between 1.18 and 1.87 times the costs of usual care. There is no clear association between the costs of interventions and either their intensity or their efficacy in reducing blood pressure. Therefore it is difficult to estimate the cost-effectiveness of nurse led interventions. One UK trial reported an incremental cost-effectiveness ratio per quality adjusted life year of £28.983 [75]; this exceeds the £20,000 implementation cost threshold set by the UK National Institute for Health and Care Excellence [109].

18.4 Clinical Implications

The findings of individual trials and systematic reviews summarised here offer some guidance for the design of a successful nurse led programme for care in hypertension. Contacts should be face to face, occurring at least monthly until blood pressure reaches target. They should include the ability to either prescribe, or advise the doctor to prescribe, changes in blood pressure lowering medications and be guided by a structured stepped care algorithm. Lowering of systolic blood pressure by 5 mmHg has been estimated to lead to 14% fewer deaths from stroke, 9% fewer deaths from CHD, and 7% fewer deaths overall [110]. These levels of reduction are exceeded by

the most intensive nurse led interventions so are clinically as well as statistically important.

There are clinical reasons to favour rapid and effective control of blood pressure; arterial stiffness, a marker of target organ damage, improves in newly diagnosed and treated hypertensives according to the intensity of BP lowering achieved [111]. Similarly post hoc findings from the VALUE trial found that blood pressure response within 1 month of treatment predicted a persistent advantage for the combined outcome of cardiac events, stroke or death [112, 113], and post hoc analysis of the Syst-Eur trial provided additional evidence for improved outcomes in cardiovascular event reduction for initial dual rather than monotherapy, in association with greater blood pressure reduction [114]. The FEVER study also suggests superior outcomes for early attainment of blood pressure control in a Chinese population [115]. None of these findings, however, relate directly to nurse led interventions to control blood pressure, and evidence for long-term differences in outcome for nurse led care is currently lacking.

Extrapolation of trial findings into day-to-day practice cannot be assumed. Little is known about the acceptability of substitution of nurse led for doctor led care in hypertension. Exploratory findings in our locality suggest that the concept is broadly acceptable to patients [116], as is the case for nurse prescribing in diabetes, a condition often associated with hypertension [117]. However despite good trial evidence for improved blood pressure lowering with nurse prescribing we could not confirm this benefit in a recent analysis of routine primary care data from our region [19].

18.5 Research Implications

In trials (and in practice), nurses often work in conjunction with other members of the primary health care team such as community health workers, health care assistants [19], pharmacists and doctors [118]. Many trials provide evidence for improved outcomes with pharmacist led care [119] but few have examined a team approach utilising both nurses' and pharmacists' expertise [120, 121]. Community health workers or lay workers have sometimes been included in trials of interventions [56, 71], often in low resource settings or with a specific role in link working with specific ethnic groups who may experience barriers to accessing care [80, 81]. Studies suggest that teams can facilitate self-management [122], and a recent survey of routine primary care data in our region has documented the increasing involvement of health care assistants in team approaches to hypertension care with better attainment of the English national Quality and Outcomes Framework blood pressure target [19, 123]. Future studies need to examine team based approaches that make best use of existing professionals' and multidisciplinary teams' skills, thus facilitating adoption into existing care structures; some such studies are underway [124, 125].

The available evidence suggests that future trials should abandon telephone support as a component of any intervention; however, internet or other telehealth systems may show benefits [82, 126, 127]. It is possible that nurses may enhance the

benefits of home or telemonitoring but their specific role and contribution requires further study [101, 128].

It seems clear that any prospective study design should be resourced for at least a monthly face to face review until blood pressure control is achieved, and should include the ability to prescribe or alter medication according to a stepped care algorithm. Depending on study setting, a careful study design will be required to mitigate the effects of setting (home vs. clinic) and personnel (nurse vs. doctor vs. pharmacist) on white coat effects to minimise bias. Ideally future studies will be designed and powered to measure costs and cost-effectiveness of interventions, and measure satisfaction and treatment effects using validated tools.

International blood pressure guideline targets are starting to be cut in response to evidence from SPRINT and other recent studies [129–132]. Currently evidence of greater blood pressure lowering only exists for nurse led care down to, but not below, 130 mmHg systolic in the context of comorbidities such as diabetes or secondary prevention of cardiovascular and cerebrovascular disease [25, 49, 52, 60, 61, 74, 75, 82, 83]. It will be important to test nurse led interventions that aim to cut blood pressure to lower more stringent potential targets in primary prevention, to discover whether the existing evidence can be extrapolated.

The reporting of harms from nurse led intervention studies is negligible. Although such interventions are expected to offer a low risk of adverse events, this should be confirmed by robust reporting and inclusion of quality of life and satisfaction scales in future studies. Again the implications of increased adverse events seen in trials aiming to lower blood pressure below 130 mmHg will have to be taken into account [129, 133].

Conclusions

There is good evidence to suggest that nurse led interventions can achieve greater blood pressure reductions and achievement of blood pressure targets than usual care. Reviewing patients at least monthly, and changing medication according to a stepped care protocol are shown to be important elements of such interventions. Inclusion of nurses as members or leaders of teams intervening to control blood pressure should be effective but requires further study. Costs and cost benefits of interventions are poorly described and there are no reports of long-term effects of outcomes. The ability of nurse led services to adopt new lower blood pressure targets safely may be assumed but cannot currently be demonstrated. Areas for future research are identified.

Acknowledgments The analyses presented are based on data collected for our Cochrane review: Allied health professional led interventions for improving control of blood pressure in patients with hypertension (A115). The review has been submitted and publication is anticipated during 2018. I thank my co-authors for their contributions to the review: Lyne Cloutier, Shweta Todkar, Judit Konya, Olivia Clark, Sinead McDonagh, Lindsay Smith, Liam Glynn, Rod Taylor and John Campbell. *Disclosure*: Christopher Clark is supported by a National Institute of Health Research (NIHR) Clinical Lectureship award. The views expressed are those of the author and not necessarily those of the NIHR, the NHS or the Department of Health.

References

1. Naghavi M, Wang HD, Lozano R, et al. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet. 2015;385(9963):117–71.
2. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet. 2005;365(9455):217–23.
3. National Centre for Social Research. Health survey for England: 2010. Department of, Epidemiology & Public Health. U. C. L. Medical School: NHS Information Centre for health and social care; 2012.
4. Kringos D, Boerma W, Bourgueil Y, et al. The strength of primary care in Europe: an international comparative study. Br J Gen Pract. 2013;63(616):e742–50.
5. Bodenheimer T, Pham HH. Primary care: current problems and proposed solutions. Health Aff. 2010;29(5):799–805.
6. Hobbs FD, Bankhead C, Mukhtar T, et al. Clinical workload in UK primary care: a retrospective analysis of 100 million consultations in England, 2007-14. Lancet. 2016;387(10035):2323–30.
7. Laurant M, Reeves D, Hermens R, Braspenning J, Grol R, Sibbald B. Substitution of doctors by nurses in primary care. Cochrane Database Syst Rev. 2005;(2):Cd001271.
8. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009;338:b1665.
9. Falaschetti E, Mindell J, Knott C, Poulter N. Hypertension management in England: a serial cross-sectional study from 1994 to 2011. Lancet. 2014;383(9932):1912–9.
10. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension. J Hypertens. 2013;31:1281–357.
11. Alanen S, Ijas J, Kaila M, Makela M, Valimaki M. Hypertension guideline implementation: experiences of Finnish primary care nurses. J Eval Clin Pract. 2008;14(5):830–5.
12. Goodwin JS, Kuo Y. Growth of nurse practitioners as primary care providers for the elderly. J Am Geriatr Soc. 2012;60:S4–5.
13. Lovink MH, Persoon A, Koopmans RT, Van Vught AJ, Schoonhoven L, Laurant MG. Effects of substituting nurse practitioners, physician assistants or nurses for physicians concerning healthcare for the ageing population: a systematic literature review. J Adv Nurs. 2017;73(9):2084–102.
14. Logan AG, Milne BJ, Achber C, Campbell WP, Haynes RB. Work-site treatment of hypertension by specially trained nurses. A controlled trial. Lancet. 1979;2(8153):1175–8.
15. Jewell D, Hope J. Evaluation of a nurse-run hypertension clinic in general practice. Practitioner. 1988;232(1447):484–7.
16. Robson J, Boomla K, Fitzpatrick S, et al. Using nurses for preventive activities with computer assisted follow up: a randomised controlled trial. BMJ. 1989;298(6671):433–6.
17. Glynn LG, Murphy AW, Smith SM, Schroeder K, Fahey T. Interventions used to improve control of blood pressure in patients with hypertension. Cochrane Database Syst Rev. 2010;(3):CD005182. Chichester: Wiley.
18. Clark CE, Smith LFP, Taylor RS, Campbell JL. Nurse led interventions to improve control of blood pressure in people with hypertension: systematic review and meta-analysis. BMJ. 2010;341:c3995.
19. Mejzner N, Clark CE, Smith LF, Campbell JL. Trends in the diagnosis and management of hypertension: repeated primary care survey in South West England. Br J Gen Pract. 2017;67(658):e306–13.
20. Potthoff SA, Vonend O. Multidisciplinary approach in the treatment of resistant hypertension. Curr Hypertens Rep. 2017;19(1):9.
21. Clark CE, Horvath IA, Taylor RS, Campbell JL. Doctors record higher blood pressures than nurses: systematic review and meta-analysis. Br J Gen Pract. 2014;64(621):e223–32. https://doi.org/10.3399/bjgp14X677851.

22. Mancia G, Parati G, Pomidossi G, Grassi G, Casadei R, Zanchetti A. Alerting reaction and rise in blood pressure during measurement by physician and nurse. Hypertension. 1987;9(2):209–15.
23. Bengtson A, Drevenhorn E. The nurse's role and skills in hypertension care: a review. Clin Nurse Spec. 2003;17(5):260–8.
24. Clark CE, Smith LFP, Glynn L, Taylor RS, Campbell JL. Allied health professional-led interventions for improving control of blood pressure in patients with hypertension [Protocol]. Cochrane Database Syst Rev. 2011. Chichester: Wiley.
25. Brennan T, Spettell C, Villagra V, et al. Disease management to promote blood pressure control among African Americans. Popul Health Manag. 2010;13:65–72.
26. Contreras EM, Garcia OV, Claros NM, et al. Efficacy of telephone and mail intervention in patient compliance with antihypertensive drugs in hypertension. ETECUM-HTA study. Blood Press. 2005;14(0803-7051 (Print), 0803-7051 (Linking), 3):151–8.
27. Janssen PG, Gorter KJ, Stolk RP, Rutten GE. Randomised controlled trial of intensive multifactorial treatment for cardiovascular risk in patients with screen-detected type 2 diabetes: 1-year data from the ADDITION Netherlands study. Br J Gen Pract. 2009;59(558):43–8.
28. Odnoletkova I, Goderis G, Nobels F, et al. Optimizing diabetes control in people with Type 2 diabetes through nurse-led telecoaching. Diabet Med. 2016;33(6):777–85.
29. Dean SC, Kerry SM, Khong TK, Kerry SR, Oakeshott P. Evaluation of a specialist nurse-led hypertension clinic with consultant backup in two inner city general practices: randomized controlled trial. Fam Pract. 2014;31(2):172–9.
30. Khalid A, Shan W, David C, et al. Experience from a pilot study of a nurse-led hypertension clinic in general practice. J Eval Clin Pract. 2011;17:1239–42.
31. Ester AG, Enriqueta PR, Valeria PH, et al. Knowledge and adherence to antihypertensive therapy in primary care: results of a randomized trial. Asian J Pharm Clin Res. 2011;25:62–7.
32. Bebb C, Kendrick D, Coupland C, et al. A cluster randomised controlled trial of the effect of a treatment algorithm for hypertension in patients with type 2 diabetes. Br J Gen Pract. 2007;57(535):136–43.
33. Bogner HR, de Vries HF, Kaye EM, Morales KH. Pilot trial of a licensed practical nurse intervention for hypertension and depression. Fam Med. 2013;45(5):323–9.
34. Bosworth HB, Olsen MK, Dudley T, et al. Patient education and provider decision support to control blood pressure in primary care: a cluster randomized trial. Am Heart J. 2009;157:450–6.
35. Bosworth HB, Olsen MK, Grubber JM, et al. Two self-management interventions to improve hypertension control: a randomized trial. Ann Intern Med. 2009;151:687–95.
36. Chiu CW, Wong FK. Effects of 8 weeks sustained follow-up after a nurse consultation on hypertension: a randomised trial. Int J Nurs Stud. 2010;47:1374–82.
37. Crowley MJ, Powers BJ, Olsen MK, et al. The cholesterol, hypertension, and glucose education (CHANGE) study: results from a randomized controlled trial in African Americans with diabetes. Am Heart J. 2013;166:179–86.
38. Edelman D, Dolor RJ, Coffman CJ, et al. Nurse-led behavioral management of diabetes and hypertension in community practices: a randomized trial. J Gen Intern Med. 2015;30(5):626–33.
39. Jolly K, Bradley F, Sharp S, et al. Randomised controlled trial of follow up care in general practice of patients with myocardial infarction and angina: final results of the Southampton heart integrated care project (SHIP). The SHIP Collaborative Group. BMJ. 1999;318(7185):706–11.
40. Kastarinen MJ, Puska PM, Korhonen MH, et al. Non-pharmacological treatment of hypertension in primary health care: a 2-year open randomized controlled trial of lifestyle intervention against hypertension in eastern Finland. J Hypertens. 2002;20(0263-6352 (Print), 12):2505–12.
41. Moher M, Yudkin P, Wright L, et al. Cluster randomised controlled trial to compare three methods of promoting secondary prevention of coronary heart disease in primary care. BMJ. 2001;322(0959-8138 (Print), 7298):1338.

42. Polgreen LA, Han J, Carter BL, et al. Cost-effectiveness of a physician-pharmacist collaboration intervention to improve blood pressure control. Hypertension. 2015;66(6):1145–51.
43. Rinfret S, Lussier MT, Peirce A, et al. The impact of a multidisciplinary information technology-supported program on blood pressure control in primary care. Circ Cardiovasc Qual Outcomes. 2009;2(3):170–7.
44. Schroeder K, Fahey T, Hollinghurst S, Peters TJ. Nurse-led adherence support in hypertension: a randomized controlled trial. Fam Pract. 2005;22(2):144–51.
45. Sen M, Rasjo Wraak G, Ronmark P, et al. Lack of long-term effects from a pedagogical intervention upon blood pressure control—a randomized primary care study. Scand Cardiovasc J. 2013;47(5):289–96.
46. Woollard J, Beilin L, Lord T, Puddey I, MacAdam D, Rouse I. A controlled trial of nurse counselling on lifestyle change for hypertensives treated in general practice: preliminary results. Clin Exp Pharmacol Physiol. 1995;22(6–7):466–8.
47. Woollard J, Burke V, Beilin LJ. Effects of general practice-based nurse-counselling on ambulatory blood pressure and antihypertensive drug prescription in patients at increased risk of cardiovascular disease. J Hum Hypertens. 2003;17(10):689–95.
48. Artinian NT, Flack JM, Nordstrom CK, et al. Effects of nurse-managed telemonitoring on blood pressure at 12-month follow-up among urban African Americans. Nurs Res. 2007;56(0029-6562 (Print), 5):312–22.
49. Tobe SW, Pylypchuk G, Wentworth J, et al. Effect of nurse-directed hypertension treatment among First Nations people with existing hypertension and diabetes mellitus: the Diabetes Risk Evaluation and Microalbuminuria (DREAM 3) randomized controlled trial. CMAJ. 2006;174(1488-2329 (Electronic), 9):1267–71.
50. Zhu X, Wong FKY, Wu LH. Development and evaluation of a nurse-led hypertension management model in a community: a pilot randomized controlled trial. Int J Clin Exp Med. 2014;7(11):4369–77.
51. Hornnes N, Larsen K, Boysen G. Blood pressure 1 year after stroke: the need to optimize secondary prevention. J Stroke Cerebrovasc Dis. 2011;20:16–23.
52. Kerry SM, Markus HS, Khong TK, et al. Home blood pressure monitoring with nurse-led telephone support among patients with hypertension and a history of stroke: a community-based randomized controlled trial. CMAJ: Can Med Assoc J. 2013;185(1):23–31.
53. Rudd P, Miller NH, Kaufman J, et al. Nurse management for hypertension. A systems approach. Am J Hypertens. 2004;17(10):921–7.
54. Artinian NT, Washington OG, Templin TN. Effects of home telemonitoring and community-based monitoring on blood pressure control in urban African Americans: a pilot study. Heart Lung. 2001;30(3):191–9.
55. Allen JK, Dennison Himmelfarb CR, Szanton SL, Frick KD. Cost-effectiveness of nurse practitioner/community health worker care to reduce cardiovascular health disparities. J Cardiovasc Nurs. 2014;29(4):308–14.
56. Becker DM, Yanek LR, Johnson WR Jr, et al. Impact of a community-based multiple risk factor intervention on cardiovascular risk in black families with a history of premature coronary disease. Circulation. 2005;111(10):1298–304.
57. Cooper J, Zimmerman W. The effect of a faith community nurse network and public health collaboration on hypertension prevention and control. Public Health Nurs (Boston, MA). 2017;34(5):444–53.
58. Lee LL, Arthur A, Avis M. Evaluating a community-based walking intervention for hypertensive older people in Taiwan: a randomized controlled trial. Prev Med. 2007;44(2):160–6.
59. Denver EA, Barnard M, Woolfson RG, Earle KA. Management of uncontrolled hypertension in a nurse-led clinic compared with conventional care for patients with type 2 diabetes. Diabetes Care. 2003;26(8):2256–60.
60. MacMahon Tone J, Agha A, Sherlock M, Finucane F, Tormey W, Thompson CJ. An intensive nurse-led, multi-interventional clinic is more successful in achieving vascular risk reduction targets than standard diabetes care. Ir J Med Sci. 2009;178:179–86.

61. Wallymahmed ME, Morgan C, Gill GV, MacFarlane IA. Nurse-led cardiovascular risk factor intervention leads to improvements in cardiovascular risk targets and glycaemic control in people with Type-1 diabetes when compared with routine diabetes clinic attendance. Diabet Med. 2011;28(3):373–9.
62. Ko GT, Li JK, Kan EC, Lo MK. Effects of a structured health education programme by a diabetic education nurse on cardiovascular risk factors in Chinese Type 2 diabetic patients: a 1-year prospective randomized study. Diabet Med. 2004;21(12):1274–9.
63. Litaker D, Mion L, Planavsky L, Kippes C, Mehta N, Frolkis J. Physician—nurse practitioner teams in chronic disease management: the impact on costs, clinical effectiveness, and patients' perception of care. J Interprof Care. 2003;17(3):223–37.
64. McHugh F, Lindsay GM, Hanlon P, et al. Nurse led shared care for patients on the waiting list for coronary artery bypass surgery: a randomised controlled trial. Heart. 2001;86(1468-201X (Electronic), 3):317–23.
65. Campbell NC, Ritchie LD, Thain J, Deans HG, Rawles JM, Squair JL. Secondary prevention in coronary heart disease: a randomised trial of nurse led clinics in primary care. Heart. 1998;80(5):447–52.
66. Mackenzie G, Ireland S, Moore S, et al. Tailored interventions to improve hypertension management after stroke or TIA—phase II (TIMS II). Can J Neurosci Nurs. 2013;35:27–34.
67. Hebert PL, Sisk JE, Tuzzio L, et al. Nurse-led disease management for hypertension control in a diverse urban community: a randomized trial. J Gen Intern Med. 2012;27(6):630–9.
68. Alhalaiqa F, Deane KH, Nawafleh AH, Clark A, Gray R. Adherence therapy for medication non-compliant patients with hypertension: a randomised controlled trial. J Hum Hypertens. 2011;28:117–26.
69. Logan AG, Milne BJ, Achber C, Campbell WP, Haynes RB. Cost-effectiveness of a worksite hypertension treatment program. Hypertension. 1981;3(2):211–8.
70. Logan AG, Milne BJ, Flanagan PT, Haynes RB. Clinical effectiveness and cost-effectiveness of monitoring blood pressure of hypertensive employees at work. Hypertension. 1983;5:828–36.
71. Allen JK, Dennison-Himmelfarb CR, Szanton SL, et al. Community Outreach and Cardiovascular Health (COACH) Trial: a randomized, controlled trial of nurse practitioner/community health worker cardiovascular disease risk reduction in urban community health centers. Circ Cardiovasc Qual Outcomes. 2011;4(6):595–602.
72. Garcia-Pena C, Thorogood M, Armstrong B, Reyes-Frausto S, Munoz O. Pragmatic randomized trial of home visits by a nurse to elderly people with hypertension in Mexico. Int J Epidemiol. 2001;30(6):1485–91.
73. Pezzin LE, Feldman PH, Mongoven JM, McDonald MV, Gerber LM, Peng TR. Improving blood pressure control: results of home-based post-acute care interventions. J Gen Intern Med. 2011;26:280–6.
74. Taylor CB, Miller NH, Reilly KR, et al. Evaluation of a nurse-care management system to improve outcomes in patients with complicated diabetes. Diabetes Care. 2003;26(4):1058–63.
75. Bellary S, O'Hare JP, Raymond NT, et al. Enhanced diabetes care to patients of south Asian ethnic origin (the United Kingdom Asian Diabetes Study): a cluster randomised controlled trial. Lancet. 2008;371(1474-547X (Electronic), 9626):1769–76.
76. New JP, Mason JM, Freemantle N, et al. Educational outreach in diabetes to encourage practice nurses to use primary care hypertension and hyperlipidaemia guidelines (EDEN): a randomized controlled trial. Diabet Med. 2004;21(6):599–603.
77. Bosworth HB, Powers BJ, Olsen MK, et al. Home blood pressure management and improved blood pressure control: results from a randomized controlled trial. Arch Intern Med. 2011;171:1173–80.
78. New JP, Mason JM, Freemantle N, et al. Specialist nurse-led intervention to treat and control hypertension and hyperlipidemia in diabetes (SPLINT): a randomized controlled trial. Diabetes Care. 2003;26(8):2250–5.

79. Attridge M, Creamer J, Ramsden M, Cannings-John R, Hawthorne K. Culturally appropriate health education for people in ethnic minority groups with type 2 diabetes mellitus. Cochrane Database Syst Rev. 2014;(9):CD006424.
80. Hotu C, Bagg W, Collins J, et al. A community-based model of care improves blood pressure control and delays progression of proteinuria, left ventricular hypertrophy and diastolic dysfunction in Maori and Pacific patients with type 2 diabetes and chronic kidney disease: a randomized controlled trial. Nephrol Dial Transplant. 2010;25(10):3260–6.
81. O'Hare JP, Raymond NT, Mughal S, et al. Evaluation of delivery of enhanced diabetes care to patients of South Asian ethnicity: the United Kingdom Asian Diabetes Study (UKADS). Diabet Med. 2004;21(0742-3071 (Print), 12):1357–65.
82. Wakefield BJ, Holman JE, Ray A, et al. Effectiveness of home telehealth in comorbid diabetes and hypertension: a randomized, controlled trial. Telemed J E Health. 2011;17:254–61.
83. McKee MD, Fletcher J, Sigal I, Giftos J, Schechter C, Walker EA. A collaborative approach to control hypertension in diabetes: outcomes of a pilot intervention. J Prim Care Community Health. 2011;2:148–52.
84. Tonstad S, Alm CS, Sandvik E. Effect of nurse counselling on metabolic risk factors in patients with mild hypertension: a randomised controlled trial. Eur J Cardiovasc Nurs. 2007;6(2):160–4.
85. Ulm K, Huntgeburth U, Gnahn H, Briesenick C, Prner K, Middeke M. Effect of an intensive nurse-managed medical care programme on ambulatory blood pressure in hypertensive patients. Arch Cardiovasc Dis. 2010;103:142–9.
86. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ. 2009;339:b2535.
87. Fahey T, Schroeder K, Ebrahim S. Educational and organisational interventions used to improve the management of hypertension in primary care: a systematic review. Br J Gen Pract. 2005;55(520):875–82.
88. Fahey T, Schroeder K, Ebrahim S. Interventions used to improve control of blood pressure in patients with hypertension. Cochrane Database Syst Rev (Online). 2005;(1).
89. Phillips LS, Branch WT, Cook CB, et al. Clinical inertia. Ann Intern Med. 2001;135(9):825–34.
90. Hines R, Stone NJ. Patients and physicians beliefs and practices regarding adherence to cardiovascular medication. JAMA Cardiol. 2016;1(4):470–3.
91. Ligthart SA, van den Eerenbeemt KD, Pols J, van Bussel EF, Richard E, Moll van Charante EP. Perspectives of older people engaging in nurse-led cardiovascular prevention programmes: a qualitative study in primary care in the Netherlands. Br J Gen Pract. 2015;65(630):e41–8.
92. Schroeder K, Fahey T. Improving adherence to drugs for hypertension. BMJ. 2007;335(7628):1002–3.
93. Wetzels GE, Nelemans P, Schouten JS, Prins MH. Facts and fiction of poor compliance as a cause of inadequate blood pressure control: a systematic review. J Hypertens. 2004;22(10):1849–55.
94. Nuesch R, Schroeder K, Dieterle T, Martina B, Battegay E. Relation between insufficient response to antihypertensive treatment and poor compliance with treatment: a prospective case-control study. BMJ. 2001;323:142–6.
95. Krousel-Wood M, Islam T, Webber LS, Re RN, Morisky DE, Muntner P. New medication adherence scale versus pharmacy fill rates in seniors with hypertension. Am J Manag Care. 2009;15(1):59–66.
96. Gallagher BD, Muntner P, Moise N, Lin JJ, Kronish IM. Are two commonly used self-report questionnaires useful for identifying antihypertensive medication nonadherence? J Hypertens. 2015;33(5):1108–13.
97. Prado JC Jr, Kupek E, Mion D Jr. Validity of four indirect methods to measure adherence in primary care hypertensives. J Hum Hypertens. 2007;21(7):579–84.
98. Bray EP, Holder R, Mant J, McManus RJ. Does self-monitoring reduce blood pressure? Meta-analysis with meta-regression of randomized controlled trials. Ann Med. 2010;42(5):371–86.
99. Rogers MA, Small D, Buchan DA, et al. Home monitoring service improves mean arterial pressure in patients with essential hypertension. A randomized, controlled trial. Ann Intern Med. 2001;134(11):1024–32.

100. McManus RJ, Mant J, Bray EP, et al. Telemonitoring and self-management in the control of hypertension (TASMINH2): a randomised controlled trial. Lancet. 2010;376(9736):163–72.
101. Uhlig K, Patel K, Ip S, Kitsios GD, Balk EM. Self-measured blood pressure monitoring in the management of hypertension: a systematic review and meta-analysis. Ann Intern Med. 2013;159(3):185–94.
102. Cappuccio FP, Kerry SM, Forbes L, Donald A. Blood pressure control by home monitoring: meta-analysis of randomised trials. BMJ. 2004;329(7458):145.
103. McManus, RJ, et al. Efficacy of self-monitored blood pressure, with or without telemonitoring, for titration of antihypertensive medication (TASMINH4): an unmasked randomised controlled trial. Lancet. 2018;391(10124):949–59.
104. Weeks G, George J, Maclure K, Stewart D. Non-medical prescribing versus medical prescribing for acute and chronic disease management in primary and secondary care. Cochrane Database Syst Rev. 2016;11:CD011227.
105. Jansen J, Naganathan V, Carter SM, et al. Too much medicine in older people? Deprescribing through shared decision making. BMJ. 2016;353:i2893.
106. Jordan A, Anning C, Ball C, et al. Rapid treatment of newly-diagnosed moderate-severe hypertension is safe and effective. Paper presented at: 27th European Meeting on Hypertension and Cardiovascular Protection2017; Milan.
107. Xu W, Goldberg SI, Shubina M, Turchin A. Optimal systolic blood pressure target, time to intensification, and time to follow-up in treatment of hypertension: population based retrospective cohort study. BMJ. 2015;350:h158.
108. Soghikian K. The role of nurse practitioners in hypertension care. Clin Sci Mol Med Suppl. 1978;4:345s–58s.
109. Claxton K, Martin S, Soares M, et al. Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold. Health Technol Assess (Winchester, England). 2015;19(14):1–503, v-vi.
110. Havas S, Roccella EJ, Lenfant C. Reducing the public health burden from elevated blood pressure levels in the United States by lowering intake of dietary sodium. Am J Public Health. 2004;94(1):19–22.
111. Rodilla E, Millasseau S, Costa JA, Pascual JM. Arterial destiffening in previously untreated mild hypertensives after 1 year of routine clinical management. Am J Hypertens. 2017;30(5):510–7.
112. Gradman AH, Parise H, Lefebvre P, Falvey H, Lafeuille MH, Duh MS. Initial combination therapy reduces the risk of cardiovascular events in hypertensive patients: a matched cohort study. Hypertension. 2013;61(2):309–18.
113. Weber MA, Julius S, Kjeldsen SE, et al. Blood pressure dependent and independent effects of antihypertensive treatment on clinical events in the VALUE Trial. Lancet. 2004;363(9426):2049–51.
114. Thijs L, Richart T, de Leeuw PW, et al. Morbidity and mortality on combination versus monotherapy: a posthoc analysis of the Systolic Hypertension in Europe trial. J Hypertens. 2010;28(4):865–74.
115. Liu L, Zhang Y, Liu G, Li W, Zhang X, Zanchetti A. The Felodipine Event Reduction (FEVER) Study: a randomized long-term placebo-controlled trial in Chinese hypertensive patients. J Hypertens. 2005;23(12):2157–72.
116. Clark CE, Smith LFP, Harding G, Taylor RS, Campbell JL. Nurse led hypertension clinics: evolving ahead of the evidence? J Hum Hypertens. 2011;25(S1)(10):S6.
117. Courtenay M, Stenner K, Carey N. The views of patients with diabetes about nurse prescribing. Diabet Med. 2010;27(9):1049–54.
118. Canzanello VJ, Jensen PL, Schwartz LL, Worra JB, Klein LK. Improved blood pressure control with a physician-nurse team and home blood pressure measurement. Mayo Clin Proc. 2005;80(1):31–6.
119. Santschi V, Chiolero A, Burnand B, Colosimo AL, Paradis G. Impact of pharmacist care in the management of cardiovascular disease risk factors: a systematic review and meta-analysis of randomized trials. Arch Intern Med. 2011;171(16):1441–53.

120. Leiva A, Aguilo A, Fajo-Pascual M, et al. Efficacy of a brief multifactorial adherence-based intervention in reducing blood pressure: a randomized clinical trial. Patient Prefer Adherence. 2014;8:1683–90.
121. McLean DL, McAlister FA, Johnson JA, et al. A randomized trial of the effect of community pharmacist and nurse care on improving blood pressure management in patients with diabetes mellitus: study of cardiovascular risk intervention by pharmacists-hypertension (SCRIP-HTN). Arch Intern Med. 2008;168(1538-3679 (Electronic), 21):2355–61.
122. Brownstein JN, Chowdhury FM, Norris SL, et al. Effectiveness of community health workers in the care of people with hypertension. [Review] [57 refs]. Am J Prev Med. 2007;32(5):435–47.
123. British Medical Association, NHS Employers, NHS England. 2016/17 General Medical Services (GMS) contract Quality and Outcomes Framework (QOF): guidance for GMS contract 2016/17. NHS Employers; 2016.
124. Santschi V, Wuerzner G, Chiolero A, et al. Team-based care for improving hypertension management among outpatients (TBC-HTA): study protocol for a pragmatic randomized controlled trial. BMC Cardiovasc Disord. 2017;17(1):39.
125. Maungboon P, Hutayanon P, Silaruks S. A randomized controlled trial of a trained pharmacist-nurse model care on uncomplicated hypertension in primary care setting in rural area of Thailand. J Hypertens. 2011;29:e16-Yes.
126. Qamar N, Bray EP, Glynn LG, et al. Self-monitoring for improving control of blood pressure in patients with hypertension. Cochrane Database Syst Rev. 2013;(1).
127. Salisbury C, O'Cathain A, Thomas C, et al. Telehealth for patients at high risk of cardiovascular disease: pragmatic randomised controlled trial. BMJ. 2016;353:i2647.
128. Tucker KL, Sheppard JP, Stevens R, et al. Individual patient data meta-analysis of self-monitoring of blood pressure (BP-SMART): a protocol. BMJ Open. 2015;5(9):e008532.
129. The SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015;373(22):2103–16.
130. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 7. Effects of more vs. less intensive blood pressure lowering and different achieved blood pressure levels—updated overview and meta-analyses of randomized trials. J Hypertens. 2016;34(4):613–22.
131. Gabb GM, Mangoni AA, Anderson CS, et al. Guideline for the diagnosis and management of hypertension in adults—2016. Med J Aust. 2016;205(2):85–9.
132. Leung AA, Nerenberg K, Daskalopoulou SS, et al. Hypertension Canada's 2016 Canadian hypertension education program guidelines for blood pressure measurement, diagnosis, assessment of risk, prevention, and treatment of hypertension. Can J Cardiol. 2016;32(5):569–88.
133. The ACCORD Study Group. Effects of intensive blood-pressure control in Type 2 diabetes mellitus. N Engl J Med. 2010;362(17):1575–85.

Role of the Pharmacist in Supporting Adherence

19

Marie P. Schneider and Parisa Aslani

19.1 Introduction

The high prevalence of poor medication adherence, defined as poor medication-taking behaviour, is a major issue within healthcare systems and contributes to extra morbidity/mortality and healthcare costs [1–4]. Poor medication adherence can lead to medication-related problems, many of them being preventable. In 2016, a Cochrane review showed that adherence-enhancing interventions improve short- and long-term medication adherence to lipid-lowering treatments, as well as total cholesterol and LDL-cholesterol levels [5]. Hence, nonadherence can be reduced when addressed by educated healthcare teams, pharmacists being part of them.

Pharmacists conduct clinically advanced roles in collaboration with other healthcare providers along the patient's therapeutic journey. The aim of a pharmacist's intervention is to foster patient's autonomous, ritualized and long-lasting adherent habits whenever possible. By actively engaging in patient care, pharmacists ensure rational and cost-effective use of medications to improve clinical outcomes and patient's quality of life [4]. In the era of chronic diseases and polymorbidity, community pharmacists' activities have switched from a medication-oriented activity to a patient-centred perspective in order to support patient self-management. This statement is in alignment with the joint guidelines of the International Pharmaceutical

M. P. Schneider, Ph.D., R.Ph. (✉)
Community Pharmacy, Department of Ambulatory Care and Community Medicine, University of Lausanne, Lausanne, Switzerland

Community Pharmacy, School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Lausanne, Switzerland
e-mail: Marie-paule.schneider@hospvd.ch

P. Aslani, B.Pharm.(Hons.), M.Sc., Ph.D.
Faculty of Pharmacy, The University of Sydney, Sydney, NSW, Australia
e-mail: parisa.aslani@sydney.edu.au

M. Burnier (ed.), *Drug Adherence in Hypertension and Cardiovascular Protection*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-76593-8_19

Federation (FIP) and World Health Organization (WHO) [6], and the WHO guidelines on people-centred health systems [7].

This chapter aims at describing the role of the pharmacist, in particular the community pharmacist, in addressing medication adherence in chronic patients, with a specific focus on cardiovascular patients.

19.2 Pharmacist Role and Responsibilities

The overall role of pharmacists is to validate the prescription, discuss all the relevant information on medication with the patient and make sure the patient knows, and is able to self-manage the entire treatment.

The way pharmacists address medication adherence can be categorized into two different types of support depending on patient needs: patient information/education and patient behavioural support. Pharmacists also adjust their support and interventions based on the core component of adherence being addressed: initiation, implementation or persistence [8]. In case of medication non-initiation or nonpersistence, the role of the pharmacist is primarily to facilitate the patient's understanding of their treatment benefits and refer back to physician for treatment decision making. In case of poor implementation or drug holidays, the role of the pharmacist is to understand the reasons for nonadherence and then address them appropriately to support patients in finding individualized solutions.

19.2.1 Patient Information and Education

When a patient arrives at the pharmacy with a new prescription or for a refill, the pharmacist assesses the patient's understanding of medication knowledge, and complements the information in order to reinforce the information received from the prescriber or clarifies it directly with the prescriber in case of issues [9]. The pharmacist gives information on appropriate use, rationale for use, benefits of therapy, and how to know that the medication is working. The pharmacist checks what the patient would like to know about side effects (usually very frequent or life-threatening ones) and what to do if they occur. Then, when refilling, the pharmacist checks again with the patient that he/she knows the name, the dosage, the management of each medication (what, when, how) including what to do when a dose is missed, and the aim and overall duration of the treatment.

19.2.2 Patient Behavioural Support

Pharmacists support patients in their medication self-management learning process [9]. They guide the dialogue on drug self-management by considering the patient's beliefs, experience and perspectives [10]. Changes in medication adherence have to be captured by the pharmacist as quickly as possible and gathered information must

be used to tailor treatment to patient's lifestyle. This iterative process reinforces the patient and pharmacist active partnership, increases patient's trust and satisfaction, and hence medication adherence [11].

19.3 Pharmacists' Skills and Tools to Monitor and Support Medication Adherence

To monitor and support medication adherence, pharmacist–patient interaction revolves around three pivotal axes, as described in Table 19.1: (a) communication skills to engage patients in short, repeated, individualized medication-focused interviews, (b) therapeutic actions to refine the treatment plan, and (c) use of tools and strategies, either educational and/or behavioural, to support medication adherence.

19.3.1 Communication Skills

Pharmacists are trained in communication skills. Active and reflective listening, open-ended questioning (e.g. How well does the medication work for you? How do you feel about taking this medication?) and providing information on medications by actively involving the patient are essential skills that pharmacists and the pharmacy team are asked to master to succeed in screening for medication nonadherence and in supporting self-management (see Table 19.1) [12]. Valorizing patients genuinely for their openness in expressing their views and describing their nonadherent behaviour or their efforts for overcoming nonadherence is part of the pharmacist's role in order to increase patients' trust and active partnership and keep patients in care (e.g. acknowledging the efforts that a patient with type-2 diabetes makes to take metformin 1000 mg in the morning even though he/she is unable to take it regularly in the evening) [11]. Therefore, pharmacists are developing interviewing frameworks, algorithms and toolkits to guide interviews and actions with patients [13–15].

Pharmacists are well positioned to gain information about nonadherence from patients. Patients may be more open to them than to their physician about not wanting to take medications or because they have experienced side effects. Based on patient's preference, either the pharmacist empowers and prepares the patient to inform the prescriber, or the pharmacist informs the physician.

The close location of the pharmacist to the patients in the community and their accessibility facilitate frequent and easy encounters, close patient monitoring, building up a relationship of trust and long-term follow-up (see Fig. 19.1). Moreover, the quality of the pharmacy environment facilitates an active collaboration with the patient. Indeed, a patient-centred interview can only happen if adequate privacy is ensured for one-on-one interactions at a safe distance from other patients (e.g. distant desks or confidential desk) [19]. The right to confidentiality must be protected and hence, in many countries, the community pharmacy environment is improving to address this issue.

Table 19.1 Pharmacist's communication skills, therapeutic actions, and use of tool and strategies to address medication adherence

	Communication skills[a]	Therapeutic actions	Tools and strategies
Assessing adherence	– Empathy and caring – Creating a climate of trust – Inviting patient's active participation – Exploration with reflective listening and open-ended questions – Repeated interviews over time (short but progressive) – Summarizing learned information	– Medication review – Medication reconciliation – Inquire about or measure CV risk factors (e.g. BP, lipid profile, HbA1c) – Assess adherence to cotreatments as well (e.g. antidepressant)	– Medication computerized history
Identifying causes of nonadherence		– Careful evaluation of perceived side effects	– Brief survey or questionnaire (e.g. brief medication questionnaire [16]) – Electronic smart packages – Algorithm (e.g. Pharmacist Drug Adherence Work-up Tool (DRAW) [13], TEAM [15], AIM [17], MeMO [18])
Monitoring and addressing nonadherence	– Empathy and caring – Valorization of patient's effort – Feedback on each patient's progress – Shared goal setting – Semi-structured interventions based on a framework	– Evaluate treatment appropriateness: dosage, regimen and timing – Establish a treatment plan	Educational tools: – Written information and simplified leaflets Behavioural tools: – Pill organizers – Electronic smart packages – Medication synchronization and refill reminders – mHealth – Direct observed therapy
Collaborative care	– Inform the medical team about patient's adherence over time and undertaken intervention – Social support (inviting significant other to the pharmacy)	– Discuss treatment plan with prescriber	– Inform the medical team about medication management aids used by patient

[a]Based on motivational interviewing skills; *BP* blood pressure

19.3.2 Pharmacists' Knowledge and Therapeutic Actions

Pharmacist's knowledge in the pharmaceutical sciences, pharmacotherapy and medication adherence represents the foundation for tailoring treatment to patient needs (see Fig. 19.1) [20, 21]. Pharmacists are educated in medication adherence during their curriculum; they are expected to integrate their knowledge on adherence determinants, measurement methods and interventions in their interactions with patients [22]. For example, the medication use review (MUR) involves an interview with the patient, which allows the pharmacist to review the appropriateness of the entire prescription, with the goal of improving patient's knowledge, and adherence, if necessary (see Table 19.1) [23]. The benefit of MURs outweighs their costs [24]. In terms of medication adherence, the pharmacist evaluates the appropriateness of the timing and the number of daily intakes (e.g. if the evening statin is not manageable by a patient, the pharmacist should recommend a statin with a longer half-life to be taken in the morning). The pharmacist also checks for the appropriateness of the drug formulation (e.g. ease in pill swallowing) and packages (e.g. ease in handling), and should prevent switches from one generic to another one.

In case the pharmacist detects nonadherence, he/she has to exclude the treatment as a causal factor. Indeed, professional therapeutic inertia (e.g. not addressing side effects evaluated as minor by the professional but which decrease the patient's quality of life from the patient's perspective) induces an increased risk for patient intentional nonadherence. Hence, the pharmacist ensures that there is no side effect, or in case of side effects, he/she checks that they are manageable by the patient to limit the negative impact on patient's quality of life (see Table 19.1). If a patient takes a statin erratically because of myalgia, the physician should adjust the dosage and the pharmacist should monitor patient progress to align efficacy and tolerability of the treatment as much as possible.

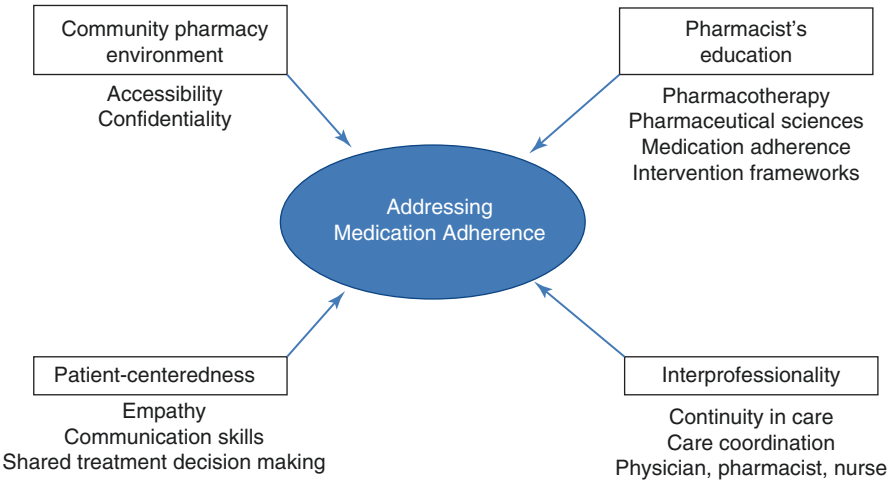


Fig. 19.1 Community pharmacist's position in the healthcare system to address medication adherence

19.3.3 Pharmacist's Medication Adherence Tools and Strategies

The pharmacist uses tools and strategies for screening and for addressing both intentional and unintentional medication nonadherence. Leaflets are part of educational strategies, whereas pillboxes, mHealth, Direct Observed Therapy (D.O.T.) and medication synchronization approaches are more behavioural (see Table 19.1).

19.3.3.1 Medication Computerized History for Screening Nonadherence

Medication computerized histories, based on dispensed treatments, are the practice-ready health records that pharmacists rely on to evaluate prescriptions from one refill to the next one (see Table 19.1). Histories have to be completed by the pharmacist through an accurate evaluation of all medications used (i.e. treatment reconciliation), particularly when the patient visits several physicians, has multiple chronic conditions and uses over-the-counter (OTC) or complementary and alternative medicines. In case the pharmacist identifies nonadherence from a patient's medication computerized history, he/she addresses and identifies the issue through a sensitive interview with the patient. The more the pharmacy develops a supportive and humanistic environment, the more the patient will feel comfortable and empowered to talk.

19.3.3.2 Medication Synchronization and Drug Refill Reminders

When delivering the treatment, pharmacists ensure medication synchronization as much as possible in order to avoid gaps in drug refills and increase refill convenience for patients. Medication synchronization means renewing all medications at the same time from the same pharmacy based on an appointment before any drug shortage occurs. First results show that synchronization improves medication adherence to cardiovascular treatments and decreases nonpersistence, especially in low adherent patients, and improves patient satisfaction [25–28].

Drug refill reminders are an option pharmacists use to retain their nonadherent patients in care [11, 29]. Late refillers either store unused drugs at home because of poor implementation or transient nonpersistence, or they are out of storage and recent nonpersisters. In both situations, the pharmacist must understand the reason of the late refilling date and support the patient accordingly.

19.3.3.3 Pill Organizers and Electronic Smart Packages

Weekly and daily pill organizers are useful for supporting patients with unintentional nonadherence, especially in case of organizational, cognitive or functional issues (e.g. elderly), in case of polypharmacy for decreasing the emotional burden of drug management or for increasing convenience of out-of-home drug intake. There is no one pill organizer model that fits all; the role of the pharmacist is to find the best model for each single patient, and inform the prescribers and healthcare teams about their pill organizer service and strategy [30]. Community pharmacists fill in pill organizers for patients, in particular for those who do not have the autonomy to do it on their own [31]. These patients come in to the pharmacy on an agreed

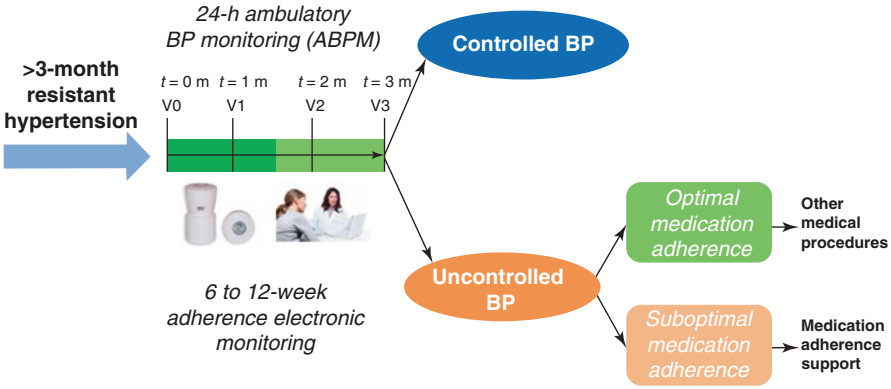


Fig. 19.2 Clinical interprofessional algorithm for the management of resistant hypertension in Lausanne University Hospital, Switzerland [33]

timetable (e.g. once a week to once a month). Patients are encouraged to leave unused medication in their pill organizer to discuss in a nonjudgmental and motivational way with the pharmacist.

Some community and primary care pharmacists use electronic smart packages (e.g. Medication Event Monitoring Systems, MEMS™, Aardex Group, Switzerland) as part of a comprehensive interprofessional service [14]. They work in close collaboration with physicians and nurses, for example in the case of resistant hypertension (see Fig. 19.2). The feedback provided by electronic monitoring is a potent way to address ingrained nonadherence issues [32].

19.3.3.4 Written Educational Material

To increase patient's medication literacy, pharmacists have the possibility to reinforce and extend oral information with written leaflets. Best leaflets should be tailored to patient's needs and support physician's information as a continuum [34, 35]. In a study in Australia, pharmacists were the preferred provider of written medication information for consumers primarily due to their medication expertise, accessibility and perceived availability [36].

19.3.3.5 mHealth

A large number of smartphone apps are available to support medication adherence. However, quality of apps varies tremendously and it is difficult, if not impossible, for patients to choose the best app needed [37]. Pharmacists can assist patients in their choice, inform them on the pros of app use (e.g. reminder system, history of drug intake and information on names and aim of treatments always at hand) and cons (e.g. privacy issues, costs). Secondly, they can also help patients introduce and update data in their app (names of drugs and regimen) at times of refill to keep the

reminder system accurate. And lastly, pharmacists can take the opportunity to review the medication history as recorded in the app at each refill. This allows opening up and steering the discussion on nonadherence issues, using motivational interviewing skills to elicit change-talk [38].

19.3.3.6 Direct Observed Therapy Combined to Clinical Outcome Measures for High-Risk Patients

Pharmacists provide Direct Observed Therapy (D.O.T.). Although D.O.T. has been initially used in withdrawal therapies (e.g. opioid, alcohol, anxiolytics) and tuberculosis, its use has been extended to transient, high-degree support of patients with serious adherence issues increasing their cardiovascular risk (e.g. resistant hypertension combined with very high blood pressure) [39, 40]. D.O.T. increases the frequency of encounters and the possibilities to identify more accurately the causes of nonadherence, and to link the effect of a better adherence to timely measured clinical outcomes (e.g. blood pressure measured at the pharmacy). D.O.T. implies a close interprofessional collaboration, notably on the adherence support strategy that should be introduced after the D.O.T. period when the clinical situation has improved to consolidate the patient's new behaviour.

19.4 Impact of Pharmacists on Medication Adherence

19.4.1 Evidence from Meta-Analysis and Systematic Reviews

There is an important body of literature showing the positive impact of pharmacist interventions to support pharmacotherapy and medication adherence in patients with cardiovascular disease (CVD). A prospective meta-analysis of randomized controlled trials (RCT) assessed the effect of pharmacist care on the management of CVD risk factors among outpatients with or without diabetes (39 RCTs, 14,224 outpatients) [41]. Compared with usual care, pharmacist interventions were associated with significant reduction in systolic (−7.6 mmHg, 95% CI: −9.0 to −6.3) and diastolic blood pressure (−3.9 mmHg, 95% CI: −5.1 to −2.8). From a public health perspective, as stated by the authors, this would reduce the risk of stroke by about 30% and myocardial infarction by 20%.

A review of 49 systematic reviews (269 RCTs) shows that clinical pharmacy services focused on specific medical conditions, such as hypertension or diabetes mellitus, revealed a positive impact on patient outcomes [42]. However interventions that targeted medication adherence specifically produced inconclusive results because of the variability of methods used to assess medication adherence and heterogeneity in terms of patient population, duration, outcomes measured and length of follow-up. The most successful pharmacist interventions to support medication adherence were multifaceted and included the use of electronic devices, a system of reminders and blister packs combined with or without education and pharmacist follow-up, concurrent oral and written information, and regular scheduled consultations with the pharmacist at the time of prescription refills.

Another systematic review (17 clinical studies) investigated the impact of interventions delivered by healthcare providers (HCPs) within a multiprofessional team (physicians and nurses, or physicians and pharmacists, or nurses and pharmacists) to improve patient adherence to cardiovascular disease medications in community settings [43]. Among the studies using only informational interventions ($n = 7$) or a combination of behavioural and informational interventions ($n = 7$), the majority showed improvements in clinical outcomes (i.e. blood pressure and total cholesterol). However, only two studies measured improvements in adherence. In contrast, all three interventions based on behaviour change strategies improved both clinical outcomes and adherence to medication.

Sapkota et al. did a systematic review (52 included studies) of interventions on adherence to anti-diabetic medications in patients with type-2 diabetes [44, 45]. The review found that multifaceted interventions (educational, behavioural, affective and/or economic) addressing several nonadherence factors (mostly related to the patient, the treatment and the disease) were comparatively more effective in improving medication adherence and glycaemic target than single strategies.

Cutrona et al. did a systematic review of RCTs of interventions in CVD or diabetes to determine the optimal modes of delivery for interventions to improve adherence to cardiovascular medications [46]. Among in-person interventions (52% successful), interventions at hospital discharge were more effective (67%) than clinic interventions (47%). In-person pharmacist interventions were effective when held in a pharmacy (83% successful), and less effective in clinics (38%). In contrast, phone calls showed low success rates (38%).

19.4.2 Insights from Selected Pharmacist Interventions on Medication Adherence

Most of the published pharmacist-led intervention studies were community-based, either in community pharmacies [15, 18, 44, 47–55] and/or primary care or hospital outpatient clinics [41, 53, 56–65]; a few were carried out at hospital discharge [13, 66, 67].

19.4.2.1 Measured Outcomes

The effectiveness of pharmacist interventions in CVD has been studied mostly in hypertension, type-2 diabetes, dyslipidemia and heart failure. The principal outcome is often evaluated on surrogate clinical endpoints or risk scores (e.g. blood pressure, haemoglobin A1c, cholesterol levels, Framingham score) [15, 47, 49, 50, 53, 59, 61, 62, 64, 66], on medication adherence [18, 48, 51, 55, 57, 58, 60, 63, 67, 68], on care utilization (emergency department care or hospitalization) [62], but less on a combination of outcomes [15, 42, 43, 56, 62, 65, 69].

19.4.2.2 Patient Inclusion Criteria

Many studies include patients with CVD whatever their adherence level and clinical outcomes [13, 47–49, 51, 54, 57, 60, 61, 66], increasing the risk of reaching the

ceiling effect of the intervention in patients with prior optimal adherence or the ones having already reached their therapeutic goals. Some studies target nonadherent populations [50, 55, 65, 68] or populations above target clinical outcomes [15, 53, 56, 59], rarely both at the same time [17]. A few studies have included patients with particular risk factors for nonadherence, e.g. treatment initiation [18], patients with low literacy or low income [62] or elderly patients [63]. In future, the impact of pharmacist-led interventions can be maximized by targeting patients with both medication nonadherence and above target clinical outcomes [55].

An important concern arising from the literature is the fact that patients declining to participate in pharmacist-led interventions, not reachable or dropping out might be the ones more in need of medication adherence interventions [47, 49, 50]. As an example, among 1596 eligible hypertensive and diabetic patients, 27% declined to participate and another 13% were unreachable; they represented an intractable group of patients with uncontrolled blood pressure (BP) [50].

19.4.2.3 Intervention Characteristics

Pharmacist-led medication adherence interventions are structured. They often combine three or four coordinated phases: (1) assessment, (2) intervention, (3) collaborative care and (4) follow-up (see Table 19.2). Each phase is organized in a three-step evaluation action plan tackling the appropriateness of the prescription, medication adherence and clinical risk factors. For example, the TEAM toolkit was developed to facilitate medication adherence, and pharmacist feedback to patients and physicians; it includes self-report adherence and a monthly assessment of core barriers, e.g. patient misunderstandings of BP goals and regimen, patient concerns about drug efficacy, adverse and long-term effects and difficulties remembering, paying, or refilling on time [15]. Compared with the control group, TEAM participants achieved greater improvements in 6-month refill adherence (60% vs. 34%, $P < 0.001$), SBP (−12.62 vs. −5.31 mmHg, $P < 0.001$) and blood pressure control (50% vs. 36%, $P = 0.01$). Six months after intervention discontinuation, TEAM participants showed sustained improvements in refill adherence ($P < 0.001$) and SBP ($P = 0.004$).

Most of the pharmacist-led interventions have lasted for 6–9 months [13, 15, 48, 49, 51, 53, 55, 57, 61, 68], and some have lasted for 12–14 months [47, 50, 58, 66]. Unfortunately, few studies have evaluated the intervention residual effect after completion [15, 50, 62]. When measured, the effect of the intervention often did not last, meaning that continued interventions are probably necessary. Frequency of pharmacist-led intervention visits is often scheduled at refill times. These visits often happen every month [15, 48, 49, 51, 58, 60], or every 2–3 months [47, 55, 57, 61, 62]. The effect of pharmacist intervention is larger if visits happen regularly, especially monthly [41, 42]. Interview sessions often last for 15–30 min [14, 47, 59, 61, 65].

19.4.2.4 Methods to Measure Adherence

The following proxy methods are used to measure medication adherence in pharmacist-led effectiveness studies: validated self-report questionnaires such as

Table 19.2 Main structural components of pharmacist-led medication adherence interventions as described in the literature

Phases	Pharmacist actions			Examples from the literature	
	A. Treatment	B. Medication adherence	C. Clinical risk factors		
Assessment	– Medication review – Medication reconciliation	– Structured screening through computerized medication history, algorithms or questionnaires – Evaluation of barriers encountered by patient	– Evaluation of CVD risk factors based on patient interview – Monitoring of CVD risk factors (e.g. BP, lipids, HbA1c)	A.	[13, 51, 55, 57, 58]
				B.	[15, 18, 47–51, 59, 61, 63]
				C.	[15, 47, 49, 50, 53, 55, 64, 70, 71]
Intervention	– Tailor or intensify medication[a]	– Patient education – Tailored adherence counselling – MI-based patient interview and patient empowerment – Use of reminder systems and pill organizers – Written education material – Written goals and action planning	– Recommendation and training on self-monitoring (e.g. BP measure)	A.	[15, 50, 53, 58, 69]
				B.	[13, 15, 18, 41, 42, 47, 49, 50, 53, 55, 57–65, 70–72]
				C.	[15, 50, 55, 61]

(continued)

Table 19.2 (continued)

Phases	Pharmacist actions			Examples from the literature	
	A. Treatment	B. Medication adherence	C. Clinical risk factors		
Collaborative care	– Involve physician for therapeutic recommendations[b] – Refer patient to physician	– Feedback to physician		A.	[15, 49, 61, 63, 66]
				B.	[15, 41, 48, 50, 58, 64, 70, 71]
Follow-up (FU)	– Reminders for prescription refill	– Arrange FU appointment – New appointment made if patient missed one – Encourage to bring empty pillboxes back – Face-to-face FU at the pharmacy or via phone calls	*(see assessment phase)*	A.	[55, 58]
				B.	[13, 15, 50, 57, 60, 61]

MI motivational interviewing, *BP* blood pressure
[a]In case pharmacists are able to prescribe, depending on the healthcare system
[b]In case, pharmacists are not able to prescribe

the Brief Medication Questionnaire (BMQ), the Medication Adherence Report Scale (MARS) or the Morisky scale [15, 47, 49, 51, 55, 59, 61, 63, 65, 67]. Refill adherence based on medication computerized history is also often used [17, 18, 50, 54, 57, 58, 63], electronic monitors are sometimes used [48, 56, 62], more rarely pill count [60] or insurance claims [68]. This implies a variety of measured adherence outcomes, moreover at various time points, generating difficulties in comparing results across studies.

19.4.2.5 Cost-Effectiveness of Pharmacist-Led Interventions

Finally, more research is needed to define the cost-effectiveness of pharmacist-led interventions in collaborative care models in patients with CVD [72]. Findings from the USA indicate that although improved medication adherence increased pharmacy costs, it also produced substantial medical savings as a result of reductions in hospitalization and emergency department use [54]. A RCT with low-income

patients with heart failure in the USA showed that medication adherence monitored electronically was 78.8% in the intervention group and 67.9% in the usual care group (difference, 10.9% [95% CI, 5.0–16.7]), emergency department visits and hospital admissions were 19.4% less (incidence rate ratio, 0.82 [CI, 0.73–0.93]) and annual direct healthcare costs were lower ($–2960 [CI, $–7603 to $1338]) in the intervention group [62]. A review (eight studies) assessed the cost-effectiveness of interventions to improve seamless care at hospital discharge focusing on medication; most studies demonstrated a positive impact on medication adherence, (re) hospitalization rates and costs [69].

Conclusion

In the cardiovascular area, a large body of evidence shows that pharmacist-led interventions in team-based care improve patient adherence to chronic medication and/or clinical outcomes. Community pharmacists are highly accessible primary care providers. They screen, monitor and support medication adherence specifically and repeatedly at treatment delivery. They check for treatment appropriateness, reinforce the medical information and actively integrate patients' views over time. They screen for nonadherence based on electronic history records and support medication adherence long-term based on semi-structured motivational interviewing, and by using reminder systems, algorithms and defined strategies. Fortunately, the role of pharmacists in medication adherence is increasingly understood by physicians and nurses. However, the road is not fully paved and the profession has to keep advocating for its role, especially at the patient level to break patient reluctance to talk about their medication-taking habits.

Most importantly, pharmacists are members of formal or informal interprofessional teams. Acknowledging that medication nonadherence is not one type but multiple types, interventions have to be multifaceted, dynamic and long-term along the patient's clinical itinerary [73]. Therefore, the sequential HCPs in charge of the patient should address medication adherence according to their expertise and time-point interventions. In the immediate future, there is a need to define the complementary roles and the specific actions of physicians, pharmacists and nurses. Obviously, addressing medication adherence interprofessionally also implies sharing medication adherence information through electronic health records to limit redundancy of actions and strengthen complementarities.

Despite the evidence on the effectiveness of pharmacist-led interventions, few programmes have been implemented in real-world settings [14, 73, 74]. There is an urgent need to make this translation possible by means of the implementation sciences. Prerequisites are necessary, especially HCPs interprofessional education in medication adherence, new policies and systems of remuneration of advanced services. Among others, the European Society for Patient Adherence, COMpliance and Persistence (ESPACOMP) is fostering this change to contribute to the viability of the healthcare system of the twenty-first century.

References

1. Cutler DM, Everett W. Thinking outside the pillbox—medication adherence as a priority for health care reform. N Engl J Med. 2010;362(17):1553–5.
2. Bosworth HB, Granger BB, Mendys P, Brindis R, Burkholder R, Czajkowski SM, et al. Medication adherence: a call for action. Am Heart J. 2011;162(3):412–24.
3. Chiatti C, Sustacchini S, Furneri G, Mantovani L, Cristiani M, Misuraca C, et al. The economic burden of inappropriate drug prescribing, lack of adherence and compliance, adverse drug events in older people a systematic review. Drug Saf. 2012;35:73–87.
4. Dalton K, Byrne S. Role of the pharmacist in reducing healthcare costs: current insights. Integr Pharm Res Pract. 2017;6:37–46.
5. van Driel ML, Morledge MD, Ulep R, Shaffer JP, Davies P, Deichmann R. Interventions to improve adherence to lipid-lowering medication. Cochrane Database Syst Rev. 2016;12:CD004371.
6. Joint FIP/WHO Guidelines on GPP: standards for quality of pharmacy services. 2011.
7. WHO Framework on integrated people-centred health services [23.08.2017]. http://www.who.int/servicedeliverysafety/areas/people-centred-care/en/.
8. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol. 2012;73(5):691–705.
9. Saseen JJ, Ripley TL, Bondi D, Burke JM, Cohen LJ, McBane S, et al. ACCP clinical pharmacist competencies. Pharmacotherapy. 2017;37(5):630–6.
10. Horne R, Chapman SC, Parham R, Freemantle N, Forbes A, Cooper V. Understanding patients' adherence-related beliefs about medicines prescribed for long-term conditions: a meta-analytic review of the Necessity-Concerns Framework. PLoS One. 2013;8(12):e80633.
11. Lambert-Kerzner A, Havranek EP, Plomondon ME, Fagan KM, McCreight MS, Fehling KB, et al. Perspectives of patients on factors relating to adherence to post-acute coronary syndrome medical regimens. Patient Prefer Adherence. 2015;9:1053–9.
12. Miller WR, Rollnick S. Motivational interviewing: helping people change. New York: Guilford Press; 2012. 482 p.
13. Hedegaard U, Hallas J, Ravn-Nielsen LV, Kjeldsen LJ. Process- and patient-reported outcomes of a multifaceted medication adherence intervention for hypertensive patients in secondary care. Res Social Adm Pharm. 2016;12(2):302–18.
14. Lelubre M, Kamal S, Genre N, Celio J, Gorgerat S, Hugentobler Hampai D, et al. Interdisciplinary medication adherence program: the example of a university community pharmacy in Switzerland. BioMed Res Int. 2015;2015:103546.
15. Svarstad BL, Kotchen JM, Shireman TI, Brown RL, Crawford SY, Mount JK, et al. Improving refill adherence and hypertension control in black patients: Wisconsin TEAM trial. J Am Pharm Assoc. 2013;53(5):520–9.
16. Svarstad BL, Chewning BA, Sleath BL, Claesson C. The Brief Medication Questionnaire: a tool for screening patient adherence and barriers to adherence. Patient Educ Couns. 1999;37(2):113–24.
17. Heisler M, Hofer TP, Klamerus ML, Schmittdiel J, Selby J, Hogan MM, et al. Study protocol: the Adherence and Intensification of Medications (AIM) study—a cluster randomized controlled effectiveness study. Trials. 2010;11:95.
18. Stuurman-Bieze AG, Hiddink EG, van Boven JF, Vegter S. Proactive pharmaceutical care interventions improve patients' adherence to lipid-lowering medication. Ann Pharmacother. 2013;47(11):1448–56.
19. Puspitasari HP, Aslani P, Krass I. The influence of pharmacy and pharmacist characteristics on the secondary prevention of cardiovascular disease. Int J Clin Pharm. 2015;37(5):834–43.
20. Mossialos E, Courtin E, Naci H, Benrimoj S, Bouvy M, Farris K, et al. From "retailers" to health care providers: transforming the role of community pharmacists in chronic disease management. Health Policy. 2015;119(5):628–39.

21. Scahill SL, Atif M, Babar ZU. Defining pharmacy and its practice: a conceptual model for an international audience. Integr Pharm Res Pract. 2017;6:121–9.
22. Schneider MP, Aslani P. Adherence policy, education and practice—an international perspective. Pharm Pract. 2010;8(4):209–12.
23. Hatah E, Braund R, Tordoff J, Duffull SB. A systematic review and meta-analysis of pharmacist-led fee-for-services medication review. Br J Clin Pharmacol. 2014;77(1):102–15.
24. Blenkinsopp A, Bond C, Raynor DK. Medication reviews. Br J Clin Pharmacol. 2012;74(4):573–80.
25. Doshi JA, Lim R, Li P, Young PP, Lawnicki VF, State JJ, et al. A synchronized prescription refill program improved medication adherence. Health Aff (Millwood). 2016;35(8):1504–12.
26. Nguyen E, Sobieraj DM. The impact of appointment-based medication synchronization on medication taking behaviour and health outcomes: a systematic review. J Clin Pharm Ther. 2017;42(4):404–13.
27. Andrews SB, Marcy TR, Osborn B, Planas LG. The impact of an appointment-based medication synchronization programme on chronic medication adherence in an adult community pharmacy population. J Clin Pharm Ther. 2017;42(4):461–6.
28. Krumme AA, Isaman DL, Stolpe SF, Dougherty S, Choudhry NK. Prevalence, effectiveness, and characteristics of pharmacy-based medication synchronization programs. Am J Manag Care. 2016;22(3):179–86.
29. Taitel MS, Mu Y, Gooptu A, Lou Y. Impact of late-to-refill reminder calls on medication adherence in the Medicare Part D population: evaluation of a randomized controlled study. Patient Prefer Adherence. 2017;11:373–9.
30. Mansoor SM, Krass I, Costa DS, Aslani P. Factors influencing the provision of adherence support by community pharmacists: a structural equation modeling approach. Res Social Adm Pharm. 2015;11(6):769–83.
31. Guignard E, Bugnon O. Pharmaceutical care in community pharmacies: practice and research in Switzerland. Ann Pharmacother. 2006;40(3):512–7.
32. Demonceau J, Ruppar T, Kristanto P, Hughes DA, Fargher E, Kardas P, et al. Identification and assessment of adherence-enhancing interventions in studies assessing medication adherence through electronically compiled drug dosing histories: a systematic literature review and meta-analysis. Drugs. 2013;73(6):545–62.
33. Schneider MP, Wuerner G, Celio J, Tremblay S, Burnier M. Clinical interprofessional algorithm for the management of resistant hypertension in Lausanne University Hospital, Switzerland. Personal communication 2015.
34. Dickinson R, Hamrosi K, Knapp P, Aslani P, Sowter J, Krass I, et al. Suits you? A qualitative study exploring preferences regarding the tailoring of consumer medicines information. Int J Pharm Pract. 2013;21(4):207–15.
35. Hamrosi KK, Aslani P, Raynor DK. Beyond needs and expectations: identifying the barriers and facilitators to written medicine information provision and use in Australia. Health Expect. 2014;17(2):220–31.
36. Hamrosi KK, Raynor DK, Aslani P. Enhancing provision of written medicine information in Australia: pharmacist, general practitioner and consumer perceptions of the barriers and facilitators. BMC Health Serv Res. 2014;14:183.
37. Santo K, Richtering SS, Chalmers J, Thiagalingam A, Chow CK, Redfern J. Mobile phone apps to improve medication adherence: a systematic stepwise process to identify high-quality apps. JMIR mHealth uHealth. 2016;4(4):e132.
38. Morton K, Dennison L, May C, Murray E, Little P, McManus RJ, et al. Using digital interventions for self-management of chronic physical health conditions: a meta-ethnography review of published studies. Patient Educ Couns. 2017;100(4):616–35.
39. Hameed MA, Tebbit L, Jacques N, Thomas M, Dasgupta I. Non-adherence to antihypertensive medication is very common among resistant hypertensives: results of a directly observed therapy clinic. J Hum Hypertens. 2016;30(2):83–9.

40. Ruzicka M, McCormick B, Leenen FH, Froeschl M, Hiremath S. Adherence to blood pressure-lowering drugs and resistant hypertension: should trial of direct observation therapy be part of preassessment for renal denervation? Can J Cardiol. 2013;29(12):1741.e1–3.
41. Santschi V, Chiolero A, Colosimo AL, Platt RW, Taffe P, Burnier M, et al. Improving blood pressure control through pharmacist interventions: a meta-analysis of randomized controlled trials. J Am Heart Assoc. 2014;3(2):e000718.
42. Rotta I, Salgado TM, Silva ML, Correr CJ, Fernandez-Llimos F. Effectiveness of clinical pharmacy services: an overview of systematic reviews (2000-2010). Int J Clin Pharm. 2015;37(5):687–97.
43. Mansoor SM, Krass I, Aslani P. Multiprofessional interventions to improve patient adherence to cardiovascular medications. J Cardiovasc Pharmacol Ther. 2013;18(1):19–30.
44. Sapkota S, Brien JA, Greenfield J, Aslani P. A systematic review of interventions addressing adherence to anti-diabetic medications in patients with type 2 diabetes—impact on adherence. PLoS One. 2015;10(2):e0118296.
45. Sapkota S, Brien JA, Greenfield JR, Aslani P. A systematic review of interventions addressing adherence to anti-diabetic medications in patients with Type 2 diabetes—components of interventions. PLoS One. 2015;10(6):e0128581.
46. Cutrona SL, Choudhry NK, Fischer MA, Servi A, Liberman JN, Brennan TA, et al. Modes of delivery for interventions to improve cardiovascular medication adherence. Am J Manag Care. 2010;16(12):929–42.
47. Aslani P, Rose G, Chen TF, Whitehead PA, Krass I. A community pharmacist delivered adherence support service for dyslipidaemia. Eur J Pub Health. 2011;21(5):567–72.
48. Bouvy ML, Heerdink ER, Urquhart J, Grobbee DE, Hoes AW, Leufkens HG. Effect of a pharmacist-led intervention on diuretic compliance in heart failure patients: a randomized controlled study. J Card Fail. 2003;9(5):404–11.
49. Chabot I, Moisan J, Gregoire JP, Milot A. Pharmacist intervention program for control of hypertension. Ann Pharmacother. 2003;37(9):1186–93.
50. Heisler M, Hofer TP, Schmittdiel JA, Selby JV, Klamerus ML, Bosworth HB, et al. Improving blood pressure control through a clinical pharmacist outreach program in patients with diabetes mellitus in 2 high-performing health systems: the adherence and intensification of medications cluster randomized, controlled pragmatic trial. Circulation. 2012;125(23):2863–72.
51. Krass I, Taylor SJ, Smith C, Armour CL. Impact on medication use and adherence of Australian pharmacists' diabetes care services. J Am Pharm Assoc (2003). 2005;45(1):33–40.
52. Lowrie R, Johansson L, Forsyth P, Bryce SL, McKellar S, Fitzgerald N. Experiences of a community pharmacy service to support adherence and self-management in chronic heart failure. Int J Clin Pharm. 2014;36(1):154–62.
53. Marra C, Johnston K, Santschi V, Tsuyuki RT. Cost-effectiveness of pharmacist care for managing hypertension in Canada. Can Pharm J/Revue des pharmaciens du Canada. 2017;150(3):184–97.
54. Roebuck MC, Liberman JN, Gemmill-Toyama M, Brennan TA. Medication adherence leads to lower health care use and costs despite increased drug spending. Health Aff (Millwood). 2011;30(1):91–9.
55. Stewart K, George J, Mc Namara KP, Jackson SL, Peterson GM, Bereznicki LR, et al. A multifaceted pharmacist intervention to improve antihypertensive adherence: a cluster-randomized, controlled trial (HAPPy trial). J Clin Pharm Ther. 2014;39(5):527–34.
56. Burnier M, Schneider MP, Chiolero A, Stubi CL, Brunner HR. Electronic compliance monitoring in resistant hypertension: the basis for rational therapeutic decisions. J Hypertens. 2001;19(2):335–41.
57. Hedegaard U, Kjeldsen LJ, Pottegard A, Henriksen JE, Lambrechtsen J, Hangaard J, et al. Improving medication adherence in patients with hypertension: a randomized trial. Am J Med. 2015;128(12):1351–61.
58. Ho PM, Lambert-Kerzner A, Carey EP, Fahdi IE, Bryson CL, Melnyk SD, et al. Multifaceted intervention to improve medication adherence and secondary prevention measures after

acute coronary syndrome hospital discharge: a randomized clinical trial. JAMA Intern Med. 2014;174(2):186–93.
59. Jarab AS, Alqudah SG, Mukattash TL, Shattat G, Al-Qirim T. Randomized controlled trial of clinical pharmacy management of patients with type 2 diabetes in an outpatient diabetes clinic in Jordan. J Manag Care Pharm. 2012;18(7):516–26.
60. Mino-Leon D, Reyes-Morales H, Flores-Hernandez S. Effectiveness of involving pharmacists in the process of ambulatory health care to improve drug treatment adherence and disease control. J Eval Clin Pract. 2015;21(1):7–12.
61. Morgado M, Rolo S, Castelo-Branco M. Pharmacist intervention program to enhance hypertension control: a randomised controlled trial. Int J Clin Pharm. 2011;33(1):132–40.
62. Murray MD, Young J, Hoke S, Tu W, Weiner M, Morrow D, et al. Pharmacist intervention to improve medication adherence in heart failure: a randomized trial. Ann Intern Med. 2007;146(10):714–25.
63. Neto PR, Marusic S, de Lyra Junior DP, Pilger D, Cruciol-Souza JM, Gaeti WP, et al. Effect of a 36-month pharmaceutical care program on the coronary heart disease risk in elderly diabetic and hypertensive patients. J Pharm Pharm Sci. 2011;14(2):249–63.
64. Santschi V, Tsuyuki RT, Paradis G. Evidence for pharmacist care in the management of hypertension. Can Pharm J/Revue des pharmaciens du Canada. 2015;148(1):13–6.
65. Wong MC, Liu KQ, Wang HH, Lee CL, Kwan MW, Lee KW, et al. Effectiveness of a pharmacist-led drug counseling on enhancing antihypertensive adherence and blood pressure control: a randomized controlled trial. J Clin Pharmacol. 2013;53(7):753–61.
66. Al Mazroui NR, Kamal MM, Ghabash NM, Yacout TA, Kole PL, McElnay JC. Influence of pharmaceutical care on health outcomes in patients with Type 2 diabetes mellitus. Br J Clin Pharmacol. 2009;67(5):547–57.
67. Stange D, Kriston L, von-Wolff A, Baehr M, Dartsch DC. Reducing cardiovascular medication complexity in a German university hospital: effects of a structured pharmaceutical management intervention on adherence. J Manag Care Pharm. 2013;19(5):396–407.
68. Abughosh SM, Wang X, Serna O, Henges C, Masilamani S, Essien EJ, et al. A pharmacist telephone intervention to identify adherence barriers and improve adherence among nonadherent patients with comorbid hypertension and diabetes in a Medicare Advantage Plan. J Manag Care Spec Pharm. 2016;22(1):63–73.
69. Simoens S, Spinewine A, Foulon V, Paulus D. Review of the cost-effectiveness of interventions to improve seamless care focusing on medication. Int J Clin Pharm. 2011;33(6):909–17.
70. Santschi V, Chiolero A, Paradis G, Colosimo AL, Burnand B. Pharmacist interventions to improve cardiovascular disease risk factors in diabetes: a systematic review and meta-analysis of randomized controlled trials. Diabetes Care. 2012;35(12):2706–17.
71. Santschi V, Chiolero A, Burnand B, Colosimo AL, Paradis G. Impact of pharmacist care in the management of cardiovascular disease risk factors: a systematic review and meta-analysis of randomized trials. Arch Intern Med. 2011;171(16):1441–53.
72. St Peter WL, Farley TM, Carter BL. Role of collaborative care models including pharmacists in improving blood pressure management in chronic kidney disease patients. Curr Opin Nephrol Hypertens. 2011;20(5):498–503.
73. La Caze A, Gujral G, Cottrell WN. How do we better translate adherence research into improvements in patient care? Int J Clin Pharm. 2014;36(1):10–4.
74. Marquis J, Schneider MP, Spencer B, Bugnon O, Du Pasquier S. Exploring the implementation of a medication adherence programme by community pharmacists: a qualitative study. Int J Clin Pharm. 2014;36(5):1014–22.

Integrated Approaches to Support Medication Adherence: The Case of Hypertension

20

Valérie Santschi

20.1 Poor Medication Adherence: A Major Cause of Poor Hypertension Control

Adherence to medications, defined as the extent to which patients take medication as prescribed by their healthcare professionals, is an important component in treatment efficacy, healthcare costs, and patient safety for chronic diseases, such as hypertension [1, 2]. The term adherence reflects an active involvement of patient within a therapeutic alliance with healthcare professionals rather than a passive response to physician's demand implied by compliance [1, 2].

Medication adherence is necessary for successful disease management. Nevertheless, medication non-adherence is common and increasingly recognized as a major problem in healthcare delivery. Hence, about one in four patients with cardiovascular disease or hypertension does not adhere to prescribed medication therapy [3]. The World Health Organization described poor adherence as the most important cause of uncontrolled hypertension with 50–70% of patients not taking their antihypertensive medication as prescribed [4]. Studies have consistently shown that 20–30% of medication prescriptions are never filled [5] and that many patients stop taking their medication in the first month following treatment initiation, often without informing their healthcare professional [6].

Poor adherence compromises the effectiveness of medication treatment and results in disease progression and serious complications including successive hospitalizations, greater morbidity and mortality, as well as increased use of healthcare

V. Santschi, Pharm.D., Ph.D. (✉)
La Source, School of nursing sciences, HES-SO University of Applied Sciences and Arts of Western Switzerland, Lausanne, Switzerland

Service of Nephrology and Hypertension, Lausanne University Hospital, Lausanne, Switzerland
e-mail: v.santschi@ecolelasource.ch

M. Burnier (ed.), *Drug Adherence in Hypertension and Cardiovascular Protection*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-76593-8_20

services and healthcare costs [7, 8]. In North America, it is estimated that approximately $100 billion are spent annually and $2000 are spent per patient per year in excess physician visits due to poor adherence [8]. Inadequate adherence to antihypertensive medication has been recognized as an important issue in the management of patient with resistant hypertension and is one of the major causes of poor control of hypertension in routine clinical practice [9], without substantial change in the past 50 years.

Addressing poor medication adherence is therefore of crucial importance in the management of hypertension care.

20.2 Methods to Measure Adherence

Several approaches such as pill counts, clinical reports, prescription refills, patient-reported measures, and electronic monitoring are used to investigate the patient medication-taking pattern or behavior and to provide medication adherence information to the patient and the healthcare professionals. Nevertheless, the diagnosis, detection, and assessment of poor adherence is challenging in routine clinical practice for healthcare professionals [6, 10, 11].

For example, physicians are poor judges to detect non-adherence of their patients in clinical practice [9, 11]. Asking patients to report on their own medication adherence leads to inaccurate estimates with an over-report of medication adherence due to difficulties recalling the details of their medication taking or in attempts to please their physicians [10, 11]. Examining pharmacy database records can be useful to assess medication adherence but they may not be reflective of patients' current disease or medication-taking pattern or behavior [11]. Pill counting, another measure of medication adherence, which relies on counting number of pills remaining after a prescribed period, overestimates patient medication adherence. This method is therefore not commonly used to estimate medication adherence in routine clinical care [11].

Electronic monitoring devices (EMDs), using e.g., the Medication Event Monitoring System (MEMS®, Aardex, Switzerland) a pill dispenser with electronic sensors activated by the act of opening, can be used to obtain accurate and real-time data on the patients' medication-taking behavior (e.g., data on dosing time and history, periods of discontinuation, and periods of good and poor adherence) with a feedback to patients and their healthcare providers [11–13]. The MEMS®, frequently used for clinical trials and other clinical studies, has the advantage of being the most accurate method for identifying non-adherence and an effective tool for measuring and improving patient medication adherence [13]. Nevertheless, the MEMS® is relatively expensive and each device can monitor only one medication which is a limitation for patients with multiple medications, a frequent case with older hypertensive patients. Implementing such electronic monitoring device is often time consuming, resource intensive and may not be feasible in busy clinical practice [2]. Another interesting approach that can be used in routine clinical practice is a combination of electronic monitoring device and patient's own reports [14].

Maintaining medication adherence to multiple medications is difficult among patients with chronic diseases, particularly hypertension. Indeed, a variety of reasons are responsible for non-adherence, but the most commonly reported barrier is forgetfulness [15]. An insufficient communication between patient and healthcare professional or a complex treatment increases also the risk of non-adherence to medications [16]. Knowledge of these causes could help healthcare professionals to target patients in need and to design the adequate intervention [17]. Because factors contributing non-adherence are complex and occur on multiple levels, improving adherence often requires complex interventions related to health provider or system as well as to patient to assure effectiveness [18, 19].

20.3 Interventions to Improve Medication Adherence

As reported by the World Health Organization report on medication adherence, interventions that improve medication adherence may have far greater effect on the health of the population than any improvement in medical treatments [4]. Several reviews identifying interventions for improving medication adherence [6, 19] concluded that complex, combined interventions, such as patient education and counselling, simplifying dose regimen, reminders, support from family or healthcare professionals (pharmacist-based or nurse-based intervention) are needed to bring substantial change in adherence. However, these interventions were mostly complex and not very effective for long term [19], with a modest improvement in blood pressure control among hypertensive patients [20].

In recent years, health technologies such as mobile phones, smartphone applications, text messaging, patient monitoring devices, and electronic health records have emerged as a strategy to improve medication adherence. For example, reminder packaging (pill box, blister packaged medications, weekly reminder, or single-use container) or electronic reminders (short message service, audiovisual reminder) can help patients to take their medications by providing visual or auditory cues [21, 22] and by supporting healthcare professionals in their comprehension of the dynamic of patient non-adherence. Unfortunately, these electronic reminders provide short-term and inconsistent effect on adherence [21–23]. A recent meta-analysis of randomized controlled studies found that mobile phone text messaging, an easy to use and relatively low-cost tool, may increase medication adherence in patients with chronic diseases [24], but the long-term effects on adherence and the effect on clinical outcomes, as well as the target populations, remain to be determined in real-world setting.

Digital health technologies using patient-reported outcome information (e.g., through telemonitoring, home blood pressure monitors, or patient monitor device) can help facilitate self-monitoring and communication of various clinical parameters such as blood pressure, as well as medication taking, enabling greater engagement of patients in their care and greater sharing with patients' healthcare professionals [25, 26]. For example, home blood pressure telemonitoring combining with pharmacist case management achieved better blood pressure control and better self-reported adherence compared with usual care [27].

Medication adherence suffers also from the fragmented approach by which hospitals, ambulatory care, and the different healthcare professionals intervene in patients with hypertension. Can integrated or team-based care help improve medication adherence in hypertension?

20.4 An Integrated or Team-Based Care Approach to Support Medication Adherence

There are many causes for poor blood pressure control, including e.g., suboptimal patient medication adherence. One strategy to improve blood pressure control and medication adherence is the provision of integrated care or team-based care with the involvement of nonphysician practitioners [28–30]. Pharmacists [31] and nurses [32] have been shown to be effective in the management of hypertension through team-based care.

Pharmacists are indeed highly accessible healthcare professionals and a valuable asset in the management of hypertension by providing medication management in collaboration with physicians and by supporting patient in their medication intake [31]. For example, Santschi et al. demonstrated that a collaborative model involving community pharmacists and primary care physicians focused on the management of medication adherence was feasible in the Swiss healthcare system [2] and improved long-term blood pressure control among uncontrolled hypertensive patients [13]. Nurses by providing lifestyle and health education are also helpful for the management of chronic diseases including hypertension [32] and a valuable member of team-based care at the interface of physicians and patients [33].

Further and large evidence support that integrated care or team-based care is an effective approach in the management of hypertension [28, 29] and particularly with a focus on medication adherence. A recent review of 39 randomized controlled trials of pharmacist care, working alone or in collaboration with nurse and physician, showed that patient education on medication adherence, recommendations to physicians in medication change, and medication management decreased both systolic and diastolic blood pressure among ambulatory patients in North America, Asia, Australia, and Europe [31] (Fig. 20.1).

Based on the growing evidence, the US Community Preventive Services Task Force recommended team-based care to improve hypertension care, especially when nurse and pharmacist are part of the team [28]. Team-based care is a health systems-level, organizational intervention that includes the patient, the different healthcare professionals, such as physicians, pharmacists, nurses, dieticians or other allied healthcare professionals (social workers and community health workers), working in a coordinated and collaborative partnership, each with their own expertise in enhancing patient care [8, 28].

Typically, team-based care interventions include activities to facilitate communication and coordination of care, to establish regular and structured follow-up, and to actively engage patients in their care by providing them education about hypertension medication, adherence support, and tools for self-management (including

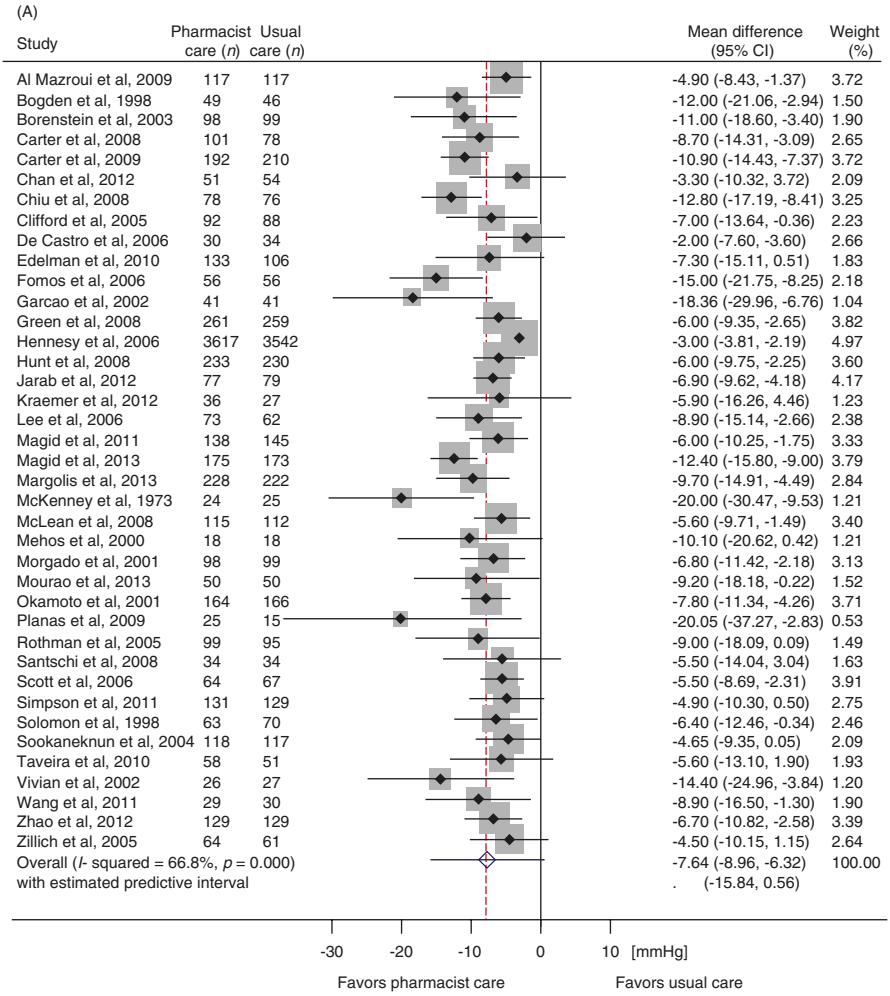


Fig. 20.1 Effect of systolic blood pressure on pharmacist interventions working alone or in collaboration with nurse or physician compared with usual care. In most of these studies, the intervention was designed notably to improve medication adherence. *n* = number of participants [31]

health behavior change) [28]. The team approach was also recommended in the last edition of the European Society of Hypertension and of Cardiology guidelines [34], with a strong emphasis on the importance of managing medication adherence.

Several community-based prevention programs involving nurses and pharmacists showed promising results. For example, Million Hearts®, a national initiative to prevent one million cardiovascular events in the USA over 5 years by implementing proven and effective interventions with the collaboration of healthcare professionals, pharmacists, hospitals, communities and individuals, may have prevented up to half a million cardiovascular events in its first 5-year phase [35]. In some

countries, community pharmacists have developed some initiatives to promote medication adherence in an integrated approach. In Quebec, ProFiL programm®, a multidisciplinary, training and communication-network program between community pharmacists and the multidisciplinary predialysis clinic, was designed to help community pharmacists to manage hypertension drug-related problems, especially on medication non-adherence, and to optimize blood pressure control among chronic kidney disease patients by sharing clinical data laboratory results, and medications [36]. Community pharmacies have also developed in their routine activity some interdisciplinary medication adherence program to support medication adherence through a motivational interviewing combined with electronic pill monitors and medication adherence report that provide feedback to patient, physician, nurse, and other pharmacists on patient's medication history [37].

In Switzerland, the Team-Based Care for improving Hypertension management (TBC-HTA) study, an ongoing 3-year pragmatic randomized controlled trial, is designed to determine whether a 6-month interprofessional intervention, involving nurses, community pharmacists, and physicians, improves blood pressure control among uncontrolled treated outpatients in routine clinical practice [38]. One key element is to improve medication adherence through a collaborative approach. More precisely, nurse and community pharmacist measure blood pressure, assess lifestyle, estimate medication adherence, and provide education to the patient about hypertension, treatment, and lifestyle. After each visit, the nurse and community pharmacist send a summary report to the physician with their recommendations related to medication adherence and lifestyle, and changes in therapy. Taking account of the nurses' and community pharmacists' recommendations, the physician adapts the treatment if necessary.

The TBC-HTA study, supported by the Health Services Research funding program of the Gottfried and Julia Bangerter-Rhyner-Stiftung and the Swiss Academy of Medical Sciences (www.samw.ch/en), is the first attempt to evaluate the impact of a team-based care on hypertension management in the Swiss primary care. This study will inform policymakers about possible implementable team-based care interventions for managing hypertension in the Swiss healthcare system, including patients' and healthcare professionals' satisfaction with the intervention [38].

Integrated or team-based care approach, e.g., through intervention based on the one evaluated in the TBC-HTA study, has the potential to respond to the challenge of medication adherence in hypertension care including support and engagement of patients, as well as coordination action among the different healthcare professionals [4].

20.5 Implementation of Integrated Care in Healthcare System

A recent survey of the NEJM Catalyst Insights Council members, a group of US executives, clinical leaders, and clinicians at organizations directly involved in healthcare delivery, underlined that care teams are the best approach to embedding patient engagement into healthcare delivery and considered the "time investment

by healthcare team" as the biggest challenge in incorporating patient engagement into care delivery [39]. One of the biggest challenges today is indeed how to design in the healthcare system a team-based care approach addressing medication adherence that engages patients, healthcare professionals of multiple institutions and sectors. Healthcare systems are very complex and the differences in professional and organizational cultures, the power relations, and the financial pressures have an impact on team-based care development, integration, and delivery in healthcare system [40].

As mentioned by the Community Preventive Services Task Force, resource allocation and reimbursement for all team members have a major impact on chronic care management, notably for the management of hypertension [28]. Strategies to maintain provider engagement such as incentives are valuable and various modalities for care communication need to be considered, including telephones and mobile phones, Internet, and new health digital technologies [28]. If policymakers and insurers fail to reward chronic care quality, improvement and implementation are difficult [41].

The implementation of team-based care implies also changes, for example in professional culture, healthcare policy, and a willingness to invest time for such a change [40]. This change in approach of care calls for interprofessional education (IPE), a collaborative approach that improves quality care outcomes and communication and coordination of team care [42, 43]. Since 2015, La Source, School of nursing sciences of the University of Applied Sciences and Arts of Western Switzerland, Lausanne, Switzerland and the Faculty of Biology and Medicine of the University of Lausanne, Switzerland developed IPE for undergraduate nursing and medical students. The aims of the IPE course entitled "Hypertension from A to Z" with a strong focus on medication adherence management are that nursing and medical students as future interprofessional team members acquire knowledge, develop common competencies in hypertension care and medication adherence care, understand the role of other healthcare professionals and his/her own role in the healthcare team, and build the value of working together in an interprofessional team. A strong focus of this course is on medication adherence measurement and management. Improving the management of hypertension throughout interprofessional education can help sharing skills and knowledge among future healthcare professionals. It also helps building a team-based care culture [44] which is the first and necessary step for interprofessional collaborative practice.

20.6 Conclusion and Perspectives

Medication adherence is a complex problem and there is no simple and ideal strategy to improve patient medication adherence in hypertension care. Integrated or team-based approach involving pharmacists and nurses represents an interesting and efficient way to help improve hypertension management and medication adherence and engage patients in their care. Innovative digital health technologies, using patient-reported outcome information (telemonitoring, home blood pressure

monitors, or patient monitor device), smartphone applications, or electronic health records may also play an important role in future hypertension care by helping medication adherence management. However, there is limited large-scale evidence to support adoption of these new digital health technologies to increase medication adherence in hypertension.

Future pragmatic research and healthcare policy changes are needed to determine the effects of an integrated care on medication adherence through interventions—using new digital health technologies—on patients-related factors (e.g., motivation, health literacy, medications), healthcare professionals-related factors (e.g., awareness, communication, treatment effectiveness), or healthcare systems-related factors (e.g., care coordination, time constraints) in real care setting. Results of such research will provide important information for policymakers and confirm whether feasibility and large-scale implementation of an integrated approach focus on medication adherence can be realized and value in improving medication adherence.

References

1. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353(5):487–97.
2. Santschi V. Adhésion au traitement médicamenteux et suivi électronique: une approche clinique de la prise en charge à long terme du patient chronique dans un réseau ambulatoire patient, pharmacien et médecin. Geneva: University of Geneva; 2007 [cited 2017 June 30]. https://doc.rero.ch/record/8014?ln=fr.
3. DiMatteo MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. Med Care. 2004;42(3):200–9.
4. World Health Organization (WHO). Adherence to long-term therapies. Evidence for action. 2003 [cited 2017 June 30]. http://www.who.int/chp/knowledge/publications/adherence_full_report.pdf.
5. Viswanathan M, Golin CE, Jones CD, Ashok M, Blalock SJ, Wines RC, Coker-Schwimmer EJ, Rosen DL, Sista P, Lohr KN. Interventions to improve adherence to self-administered medications for chronic diseases in the United States: a systematic review. Ann Intern Med. 2012;157(11):785–95.
6. Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, Agoritsas T, Mistry N, Iorio A, Jack S, Sivaramalingam B, Iserman E, Mustafa RA, Jedraszewski D, Cotoi C, Haynes RB. Interventions for enhancing medication adherence. Cochrane Database Syst Rev. 2014;(11):CD000011. https://doi.org/10.1002/14651858.CD000011.pub4. Review.
7. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. Med Care. 2005;43(6):521–30.
8. Chisholm-Burns MA, Spivey CA. The cost of medication nonadherence: consequences we cannot afford to accept. J Am Pharm Assoc (2003). 2012;52(6):823–6. https://doi.org/10.1331/JAPhA.2012.11088.
9. Burnier M, Santschi V, Favrat B, Brunner HR. Monitoring compliance in resistant hypertension: an important step in patient management. J Hypertens Suppl. 2003;21(2):S37–42.
10. Santschi V, Wuerzner G, Schneider MP, Bugnon O, Burnier M. Clinical evaluation of IDAS II, a new electronic device enabling drug adherence monitoring. Eur J Clin Pharmacol. 2007;63(12):1179–84. Epub 2007 Sept 25.
11. Gupta P, Patel P, Horne R, Buchanan H, Williams B, Tomaszewski M. How to screen for non-adherence to antihypertensive therapy. Curr Hypertens Rep. 2016;18(12):89. Review.
12. Cramer JA, Mattson RH, Prevey ML, Scheyer RD, Ouellette VL. How often is medication taken as prescribed? A novel assessment technique. JAMA. 1989;261(22):3273–7.

13. Santschi V, Rodondi N, Bugnon O, Burnier M. Impact of electronic monitoring of drug adherence on blood pressure control in primary care: a cluster 12-month randomised controlled study. Eur J Intern Med. 2008;19(6):427–34. https://doi.org/10.1016/j.ejim.2007.12.007. Epub 2008 Feb 11.
14. Vrijens B, Antoniou S, Burnier M, de la Sierra A, Volpe M. Current situation of medication adherence in hypertension. Front Pharmacol. 2017;8:100. https://doi.org/10.3389/fphar.2017.00100. eCollection 2017. Review.
15. Gadkari AS, McHorney CA. Unintentional non-adherence to chronic prescription medications: how unintentional is it really? BMC Health Serv Res. 2012;12:98.
16. Hugtenburg JG, Timmers L, Elders PJ, Vervloet M, van Dijk L. Definitions, variants, and causes of nonadherence with medication: a challenge for tailored interventions. Patient Prefer Adherence. 2013;7:675–82. https://doi.org/10.2147/PPA.S29549. Print 2013.
17. Demonceau J, Ruppar T, Kristanto P, Hughes DA, Fargher E, Kardas P, De Geest S, Dobbels F, Lewek P, Urquhart J, Vrijens B, ABC Project Team. Identification and assessment of adherence-enhancing interventions in studies assessing medication adherence through electronically compiled drug dosing histories: a systematic literature review and meta-analysis. Drugs. 2013;73(6):545–62. https://doi.org/10.1007/s40265-013-0041-3.
18. Brown MT, Bussell JK. Medication adherence: WHO cares? Mayo Clin Proc. 2011;86(4):304–14. https://doi.org/10.4065/mcp.2010.0575. Epub 2011 Mar 9.
19. Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. Cochrane Database Syst Rev. 2008;(2):CD000011. https://doi.org/10.1002/14651858.CD000011.pub3.
20. Glynn LG, Murphy AW, Smith SM, Schroeder K, Fahey T. Interventions used to improve control of blood pressure in patients with hypertension. Cochrane Database Syst Rev. 2010;(3):CD005182. https://doi.org/10.1002/14651858.CD005182.pub4. Review.
21. Vervloet M, Linn AJ, van Weert JC, de Bakker DH, Bouvy ML, van Dijk L. The effectiveness of interventions using electronic reminders to improve adherence to chronic medication: a systematic review of the literature. J Am Med Inform Assoc. 2012;19(5):696–704. https://doi.org/10.1136/amiajnl-2011-000748. Epub 2012 Apr 25.
22. Mahtani KR, Heneghan CJ, Glasziou PP, Perera R. Reminder packaging for improving adherence to self-administered long-term medications. Cochrane Database Syst Rev. 2011;(9):CD005025. https://doi.org/10.1002/14651858.CD005025.pub3.
23. Choudhry NK, Krumme AA, Ercole PM, Girdish C, Tong AY, Khan NF, Brennan TA, Matlin OS, Shrank WH, Franklin JM. Effect of reminder devices on medication adherence: the REMIND randomized clinical trial. JAMA Intern Med. 2017;177(5):624–31. https://doi.org/10.1001/jamainternmed.2016.9627.
24. Thakkar J, Kurup R, Laba TL, Santo K, Thiagalingam A, Rodgers A, Woodward M, Redfern J, Chow CK. Mobile telephone text messaging for medication adherence in chronic disease: a meta-analysis. JAMA Intern Med. 2016;176(3):340–9. https://doi.org/10.1001/jamainternmed.2015.7667. Review.
25. Steinhubl SR, Muse ED, Topol EJ. Can mobile health technologies transform health care? JAMA. 2013;310(22):2395–6. https://doi.org/10.1001/jama.2013.281078. No abstract available.
26. Zullig LL, Peterson ED, Bosworth HB. Ingredients of successful interventions to improve medication adherence. JAMA. 2013;310(24):2611–2. https://doi.org/10.1001/jama.2013.282818.
27. Margolis KL, Asche SE, Bergdall AR, Dehmer SP, Groen SE, Kadrmas HM, Kerby TJ, Klotzle KJ, Maciosek MV, Michels RD, O'Connor PJ, Pritchard RA, Sekenski JL, Sperl-Hillen JM, Trower NK. Effect of home blood pressure telemonitoring and pharmacist management on blood pressure control: a cluster randomized clinical trial. JAMA. 2013;310(1):46–56. https://doi.org/10.1001/jama.2013.6549.
28. Community Preventive Services Task Force. Team-based care to improve blood pressure control: recommendation of the Community Preventive Services Task Force. Am J Prev Med. 2014;47(1):100–2. https://doi.org/10.1016/j.amepre.2014.03.003. Epub 2014 June 2.

29. Chiolero A, Burnier M, Santschi V. Improving treatment satisfaction to increase adherence. J Hum Hypertens. 2016;30(5):295–6. https://doi.org/10.1038/jhh.2015.89. Epub 2015 Aug 20.
30. Carter BL, Rogers M, Daly J, Zheng S, James PA. The potency of team-based care interventions for hypertension: a meta-analysis. Arch Intern Med. 2009;169(19):1748–55. https://doi.org/10.1001/archinternmed.2009.316. Review.
31. Santschi V, Chiolero A, Colosimo AL, Platt RW, Taffé P, Burnier M, Burnand B, Paradis G. Improving blood pressure control through pharmacist interventions: a meta-analysis of randomized controlled trials. J Am Heart Assoc. 2014;3(2):e000718. https://doi.org/10.1161/JAHA.113.000718. Review.
32. Martínez-González NA, Tandjung R, Djalali S, Huber-Geismann F, Markun S, Rosemann T. Effects of physician-nurse substitution on clinical parameters: a systematic review and meta-analysis. PLoS One. 2014;9(2):e89181. https://doi.org/10.1371/journal.pone.0089181. eCollection 2014.
33. Santschi V, Wuerzner G, Chiolero A, Burnand B, Paradis G, Burnier M. Team-based care involving pharmacists and nurses to improve the management of hypertension. Rev Med Suisse. 2012;8(353):1694–6, 1698. Review. French.
34. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, Christiaens T, Cifkova R, De Backer G, Dominiczak A, Galderisi M, Grobbee DE, Jaarsma T, Kirchhof P, Kjeldsen SE, Laurent S, Manolis AJ, Nilsson PM, Ruilope LM, Schmieder RE, Sirnes PA, Sleight P, Viigimaa M, Waeber B, Zannad F, Redon J, Dominiczak A, Narkiewicz K, Nilsson PM, Burnier M, Viigimaa M, Ambrosioni E, Caufield M, Coca A, Olsen MH, Schmieder RE, Tsioufis C, van de Borne P, Zamorano JL, Achenbach S, Baumgartner H, Bax JJ, Bueno H, Dean V, Deaton C, Erol C, Fagard R, Ferrari R, Hasdai D, Hoes AW, Kirchhof P, Knuuti J, Kolh P, Lancellotti P, Linhart A, Nihoyannopoulos P, Piepoli MF, Ponikowski P, Sirnes PA, Tamargo JL, Tendera M, Torbicki A, Wijns W, Windecker S, Clement DL, Coca A, Gillebert TC, Tendera M, Rosei EA, Ambrosioni E, Anker SD, Bauersachs J, Hitij JB, Caulfield M, De Buyzere M, De Geest S, Derumeaux GA, Erdine S, Farsang C, Funck-Brentano C, Gerc V, Germano G, Gielen S, Haller H, Hoes AW, Jordan J, Kahan T, Komajda M, Lovic D, Mahrholdt H, Olsen MH, Ostergren J, Parati G, Perk J, Polonia J, Popescu BA, Reiner Z, Rydén L, Sirenko Y, Stanton A, Struijker-Boudier H, Tsioufis C, van de Borne P, Vlachopoulos C, Volpe M, Wood DA, Task Force Members. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34(28):2159–219. https://doi.org/10.1093/eurheartj/eht151. Epub 2013 June 14.
35. Frieden TR, Wright JS, Conway PH. Is rapid health improvement possible? Lessons from the Million Hearts initiative. Circulation. 2017;135:1677–80.
36. Santschi V, Lord A, Berbiche D, et al. Impact of collaborative and multidisciplinary care on management of hypertension in chronic kidney disease outpatients. J Pharm Health Serv Res. 2011;2:79–87.
37. Lelubre M, Kamal S, Genre N, Celio J, Gorgerat S, Hugentobler Hampai D, Bourdin A, Berger J, Bugnon O, Schneider M. Interdisciplinary medication adherence program: the example of a university community pharmacy in Switzerland. Biomed Res Int. 2015;2015:103546. https://doi.org/10.1155/2015/103546. Epub 2016 Jan 10.
38. Santschi V, Wuerzner G, Chiolero A, Burnand B, Schaller P, Cloutier L, Paradis G, Burnier M. Team-based care for improving hypertension management among outpatients (TBC-HTA): study protocol for a pragmatic randomized controlled trial. BMC Cardiovasc Disord. 2017;17(1):39. https://doi.org/10.1186/s12872-017-0472-y.
39. Volpp K, Mohta N. Patient engagement survey: how to hardwire engagement into care delivery processes. NEJM Catalyst. http://catalyst.nejm.org/patient-engagement-solutions-care-delivery-processes/. Accessed 29 June 2017.
40. Mur-Veeman I, Hardy B, Steenbergen M, Wistow G. Development of integrated care in England and the Netherlands: managing across public-private boundaries. Health Policy. 2003;65(3):227–41.

41. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness. JAMA. 2002;288(14):1775–9.
42. World Health Organization (WHO). Framework for action on interprofessional education and collaborative practice. 2010 [cited 2017 June 30]. http://www.who.int/iris/handle/10665/70185#sthash.rPdgWrmv.dpuf.
43. Institute of Medicine Committee on Quality of Health Care in America. Crossing the Quality Chasm: a new health system for the 21st century. Washington, DC: National Academy Press; 2011.
44. Santschi V, Chiolero A, Tremblay S, Delmas P, Scherrer F, Wuerzner G, Burnier M. Interprofessional education in hypertension: foundation for a team-based care culture. 10th European Public Health Conference, Stockholm, November 1–4, 2017.

Use of Apps to Improve Drug Adherence in Hypertensive Patients

21

Parati Gianfranco, Pellegrini Dario, and Torlasco Camilla

21.1 Introduction

Nowadays, arterial hypertension affects one billion people, and its prevalence is projected to be 1.5 billion in 2025. It is acknowledged as one of the most important risk factors for all-cause mortality and the leading cause for cardiovascular mortality, morbidity, as well as for disability worldwide.

Despite recent advancements in drug therapy and all the efforts made by both clinicians and scientists, hypertension control is still unsatisfactory, and inadequate compliance to prescribed treatment is still a major issue in all regions of the world. Resistant hypertension still represents a problem in a clinical setting, although "true" resistant hypertensive patients could be just a small fraction of this group, the majority of them being in reality "spurious" resistant hypertensive subjects, because of a "white coat" phenomenon or an insufficient compliance to drug therapy.

In the last decades, progress in information and communication technology (ICT) has offered new tools in the so-called eHealth field to improve patients' adherence to therapy, either by checking drug assumption (electronic blisters and card readers, ingestible sensors, electronic compliance monitors), by providing reminders for timely pill intake (by phone, email, or dedicated devices) or by improving follow-up and communication between patients and physicians (electronic records, dedicated platforms), thus also contributing to fight another major

P. Gianfranco (✉) · P. Dario · T. Camilla
Department of Medicine and Surgery, University of Milano-Bicocca, Milan, Italy

Cardiology Unit and Department of Cardiovascular, Neural and Metabolic Sciences, S. Luca Hospital, IRCCS Istituto Auxologico Italiano, Milan, Italy
e-mail: gianfranco.parati@unimib.it

M. Burnier (ed.), *Drug Adherence in Hypertension and Cardiovascular Protection*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-76593-8_21

problem represented by physician's inertia to follow the most recent hypertension management guidelines.

Despite promising results in clinical trials, these technologies have struggled to find an application in the real world of clinical practice, mainly due to the high cost of implementation and maintenance of dedicated devices and their infrastructures.

In recent years, the exponential growth of smartphone users worldwide and the fast-paced growth of health-related mobile applications have provided researchers with new tools (the so-called mHealth solutions) which might help to improve the management of hypertensive patients. Mobile applications are relatively inexpensive to develop and to implement in clinical practice and could be used to address all the aforementioned issues that limit patients' adherence to prescriptions. Preliminary studies have shown encouraging results of management strategies based on such technologies, both in terms of improving patients' compliance and of achieving blood pressure targets.

Therefore, mHealth carries the potential to represent a major advancement in the management of hypertension, with the possibility to lead to a widespread significant improvement in clinical outcomes [1]. This possibility, however, needs now to be tested by large, randomized clinical trials, that are required to provide strong evidence on the efficacy and cost-effectiveness of these ICT approaches, and—as a consequence—to support their widespread adoption in everyday practice.

21.2 eHealth and mHealth

Digital or Electronic Health (eHealth) is defined as the "*use of information and communication technologies (ICT) for health*", [1, 2] while Mobile Health (mHealth), a sub-segment of eHealth, "*covers medical and public health practice supported by mobile devices such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices*" [3].

mHealth is an emerging role-player in health management, with the potential to transform healthcare, thanks to its ease of use, broad reach, and wide acceptance [4]. In fact, smartphones diffusion is high, even in low- and middle- income countries: it has been estimated that 3.4 billion people owned a smartphone in 2016, a trend projected to be stable in the upcoming years [5]. Notably, the proportion of elderly people approaching ICT devices (the so-called late adopters) is steadily increasing. Such a developing field also includes an increasing number of applications specifically designed for smartphones. More than 100,000 mHealth apps are currently available, offering a range of functions, from personal guidance systems to health-related information collection, and to medications intake reminders. Also, many apps are connection tools to wearable devices or sensors (e.g. bracelets or watches), able to measure and store a wide range of parameters, among others heart rate, blood glucose level, blood pressure, body temperature, sleep quality and duration, and even the level of brain activities.

mHealth uses techniques and advanced concepts derived from a number of disciplines, such as computer science, electrical and biomedical engineering,

psychology, medicine, and health-related sciences [6]. Apps represent communication, information, and motivation tools and their use has been shown to increase access to health-related information, services and skills, as well as to promote positive changes in health behaviours, preventing the onset of acute and chronic diseases and improving management of chronic conditions. Adoption of these systems has opened new perspectives in the field of telemonitoring and could have a potential ground-breaking effect on daily management of hypertension, as well as of other chronic diseases [7].

21.2.1 mHealth Features

Many features make mHealth an innovative tool for patients, clinicians, and researchers.

1. The wide availability of smartphones and health-related apps allows to **reach a very high number of people**, irrespectively of geographical or socio-economical conditions, at a very moderate cost. It has been estimated that 52% of the smartphone owners use at least one mHealth app, this tendency showing a prospectively growing trend for the next few years [8]. Characteristic feature of mHealth solutions—including low cost and ubiquitous availability—have been identified in a recent document by WHO as a major drive for mHealth diffusion both in high- and low-income countries, which are trying to cut costs and to boost access to healthcare, respectively [9, 10].
2. Intrinsic smartphone equipment, such as the accelerometers, and the link to wearable sensors allow the **collection of a considerable amount of potentially relevant data on physiological and medical parameters, lifestyle features, daily activity types and intensity, as well as on environmental parameters** (e.g. on barometric pressure and altitude, air temperature, or air pollution). These data can then be used to implement evidence-driven healthcare practice interventions, based on recording, storing, and accessing "big data" in a research activity framework, and also to empower patients in caring of their clinical conditions, facilitating the access to and the understanding of their own health-related information.
3. mHealth supports the delivery of **high-quality healthcare services**, and enables personalized treatment, for example, in individuals suffering from chronic conditions, in whom collection and storage of clinical parameters (e.g. blood glucose in diabetics or blood pressure in hypertensive individuals) favour a more effective management by the physician in charge.
4. Finally, mHealth promotes the transformation of the role of patients, from passive spectators to participative actors in their own health management, while enhancing their awareness and knowledge through sensors that detect and report vital signs. This may be further strengthened by the development of ad hoc mobile apps that encourage subjects to adhere to lifestyle modifications and to drug therapy prescribed by their physicians.

21.2.2 mHealth Criticalities

As exciting as mHealth might appear, a few issues should be carefully monitored.

1. Data protection and security of health data. Unwanted sharing with third parties and inadequate safety standards for data transmission and processing, all represent violations of patients' privacy. A recent survey showed that more than 40% of apps users never cared about possible issues deriving from privacy flaws [11].
2. Lack of control and validation of the content of the apps, plus absence of proper scientific validation for some associated signal recording devices [12]. This issue may be fuelled by app stores list search results based on the popularity of apps (i.e. number of downloads and ranking provided by users), and not on scientific criteria. In this system, attractive apps can have an exponential growth and diffusion, irrespectively of the scientific background of their content. Up to now, proper regulation and standardization of mHealth technologies has not yet been achieved, posing a potential risk for patients' health. However, in February 2015 the US Food and Drug Administration (FDA) [13] released guidance recommendations for the developers and distributors of health-related apps, stating that it would enforce regulatory requirements over those apps that are designed to diagnose, treat, or to prevent a medical condition.

21.3 Smartphone Applications in Clinical Practice

Medically guided use of smartphone applications has been tested for many different purposes. Due to their nature, apps appear to be particularly suitable, from a medical point of view, as a complement for the management of chronic conditions. Indeed, the field in which more data on smartphone apps use are available is cardiovascular risk reduction, especially in the management of hypertension, weight control, physical activity, smoking cessation, diabetes, and dyslipidaemia. App developed for mHealth are in most cases designed to promote user engagement (e.g. using established design principles, conducting usability testing, or undergoing iterative development and testing).

21.3.1 Mobile Applications for Hypertension Management

Mobile apps specifically developed to focus on hypertension cover a number of topics, separately or in a comprehensive manner. Among these aspects, blood pressure values storage and sharing with health professionals are probably the most important ones, but others need to be mentioned, such as offer of educational messages, body parameters storage, physical activity tracking, drugs alert, and drug intake reminders.

21.3.1.1 Mobile Applications in Hypertension: Classification

Three main categories of apps dedicated to hypertension can be identified:

1. apps that record and store BP values manually inserted by users
2. apps with a function enabling automated transmission of BP values from the BP measurement devices to the phone
3. apps that turn the smartphone into a BP measurement device (e.g. those driving an associated cuff inflation or those offering cuffless BP measurement the latter in most cases never validated for their accuracy, however)

Apps from the first category are the most flexible and most easily available ones. Data entry can be performed in a separate moment from the reading, and they are not tied to any specific device. On the other hand, these apps expose to mistyping errors and to the subsequent inclusion of erroneous values in data record.

The second group includes apps associated to oscillometric devices (either conventional automated BP measuring devices, or specifically designed cuffs) able to automatically send data paired to the smartphone through different transmission means [14, 15]. These kind of apps are very convenient for users and assure the reliability of recorded data. On the other hand, they are linked to specific devices, with an implication of costs and poor flexibility for the end users.

The third group is at the same time the most appealing one for users, but at the same time, as exemplified by the proposal to use non-validated cuffless blood pressure measurements, it is the group raising more concerns among clinicians. The latter type of apps sometimes claim to be able to non-invasively measure BP through the analysis of the pulse wave velocity/pulse transit time [16, 17], or even without the need for any other device than the smartphone itself, by applying the subject's finger to the phone camera or to the touchscreen. Unfortunately, none of these apps has been properly validated. In some of these cases, devices offering "cuffless blood pressure readings" were considered as "prank" tools by the developers themselves. A recent study has clearly demonstrated their inaccuracy, their readings being within 15 mmHg of brachial cuff measured systolic BP and within 10 mmHg of brachial cuff measured diastolic BP only in 59% and 70% of the times, respectively, with a much larger bias in all other instances [18].

21.3.2 Mobile Applications for Compliance Improvement in Acute and Chronic Disease

Although direct assessments of drug compliance improvement through the use of mobile apps have, to our knowledge, never been performed, indirect measures of efficacy may be obtained in chronic conditions, observing the rate of target achievement.

21.3.2.1 Favouring Compliance in Obesity and Weight Management

Overweight and obesity significantly contribute to a number of health conditions, representing a significant burden on public health [19]. It has been demonstrated that a weight loss of 3–5% significantly and favourably impacts on CV risk and in particular on hypertension control as well as on the development of type 2 diabetes mellitus [20]. A lifestyle change programme, combining a reduced caloric intake, increased physical activity, and behavioural strategies, is strongly advised in obese patients [21].

mHealth strategies developed to favour weight loss include smartphone applications, handheld personal digital assistants (PDAs), and interactive voice response (IVR) systems [22, 23]. Numerous network-connected devices have also been used [24] including e-scales and wireless physical activity monitoring devices. Although many cases of non-homogeneities (different follow-up durations, inclusion of selected populations, discrepancies in sample size, simultaneous use of non-mHealth strategies) make it difficult to properly compare the results of these studies, there is a general agreement on the positive additional value of mHealth strategies, when implemented on top of the traditional strategies, in empowering obese patients and in keeping them involved in the attempts to lose weight, especially in the short and intermediate term (6 month–12 month follow-up) [25].

Five features have been identified by Khaylis et al. [23] able to effectively favour technology-based weight loss interventions, i.e.: (a) use of a structured programme, (b) self-monitoring, (c) feedback and communication, (d) social support, and (e) individual tailoring.

21.3.2.2 Favouring Compliance in Hypertension

Hypertension is one of the most important cardiovascular risk factors and its complications are considered responsible for 9.4 million deaths/year [26]. Considered its prevalence, its susceptibility to lifestyle modification and its lack of symptoms, all features that make compliance to treatment difficult to achieve, hypertension appears like a very good candidate to be approached though the help of mHealth strategies [27].

Multidisciplinary team approach, combined with dedicated counselling, have been proved effective in managing hypertensive patients, but are associated with high costs. Moreover, self-blood pressure measurement at home is currently promoted by a number of National and International Hypertension Guidelines, and is considered worldwide a useful additional tool for the management of hypertensive patients.

A small number of RCT have analysed the feasibility and efficacy of mHealth strategies, associated with self home BP measurements technologies, to achieve hypertension control in the short-to-medium term (6–12 months) [28–30]. Tested strategies include educational emails, web-based feedback [31] on reported BP values, education, and custom messages [32, 33]. Overall, studies in which the patients were adequately engaged, were educated to perform home BP self-monitoring, and were instructed to regularly and constantly use the mHealth tool provided, turned out to be successful, and a significantly better BP control was achieved in the mHealth intervention group compared to the group randomized to the traditional approach [34]. The studies able to offer a combination of patient educational

resources, timely delivery of BP data to providers, and personalized feedback messages to patients were the most successful both in terms of patients' engagement and BP results achievement, suggesting the effectiveness of this approach. In a recent meta-analysis of 13 studies (11 of which were RCTs), Liu et al. [35] compared the effects of internet-based counselling interventions on BP control in prehypertensive and hypertensive patients as compared to standard care. E-counselling interventions appeared able to reduce daytime SBP by 3.8 mmHg (95% confidence interval, −5.63 to −2.06), with a greater effect the longer the intervention. Finally, Liu et al. also found trends of greater effects when interventions used multiple behavioural techniques and were proactive with patients (as opposed to reactive or passive approaches).

Whether this multimodality eHealth approach can be as effective as a team-based in-person care, this is still to be established. The uneven sampling, the different modalities of mHealth intervention, the variability of follow-up duration and the differences in measures and outcome make it difficult to properly compare these studies results and to draw any general conclusion.

The ESH CARE APP The ESH CARE App is a validated smartphone/tablet application with informative content developed and endorsed by the Italian Society of Hypertension (SIIA) and by the European Society of Hypertension (ESH). It offers many of the functionalities described in successful intervention studies, such as support to BP self-monitoring and BP values recording, possibility of easy data communication to the physician in charge, general health and social support, and individual tailoring of proposed interventions on lifestyle changes. BP and body weight data collected by this APP and/or through a home personal computer-based system can be stored and emailed to the physician in charge at any preselected time interval. It also allows a precise management of patient's drug treatment with alarm reminders. Finally, it represents an educational tool, as it clearly summarizes practical indications coming from the European hypertension management guidelines and also includes a "question and answer" section, where most common questions about hypertension are managed, thus offering a "general overview" of all practical issues that are related to this condition. The ESH CARE APP also improves health facilities accessibility by providing an interactive list of ESH excellence centres all over Europe, together with the necessary contact information. This APP was launched during the 2015 ESH annual meeting in Milan [36] and is now being tested in a number of clinical settings. In particular, a management strategy based on the combined use of the mobile app ESH CARE and the online platform "Misuriamo", the latter designed to organize the data sent by the patients to the physician, and to combine them with the patient's health information already available in the doctor's computer, has been tested in a pilot study in Northern Italy [37]. Nine general practitioners randomized 690 consecutive uncontrolled hypertensive patients either to usual care or to this eHealth-based strategy for management. At 6 months, Office BP control (BP <140/90 mmHg) was 40.0% in control group, and 72.3% in the eHealth-managed group. At the same time, home BP control (BP <135/85 mmHg as an average of 6 days) in the eHealth group was as high as 87.5%, thus strongly supporting the favourable impact of this ICT strategy on a better hypertension management [37] (Figs. 21.1 and 21.2).

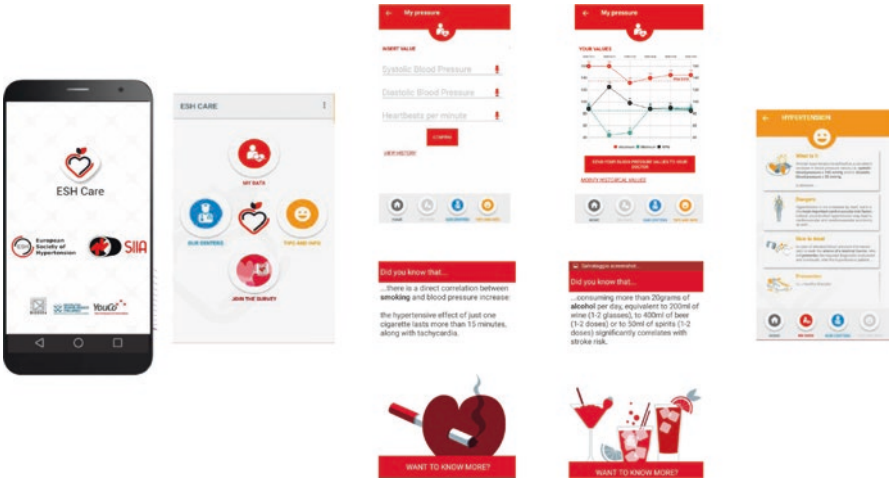


Fig. 21.1 ESH CARE App screenshots showing pages devoted to BP data input and graphic display and pages dedicated to patients education on correct lifestyle issues

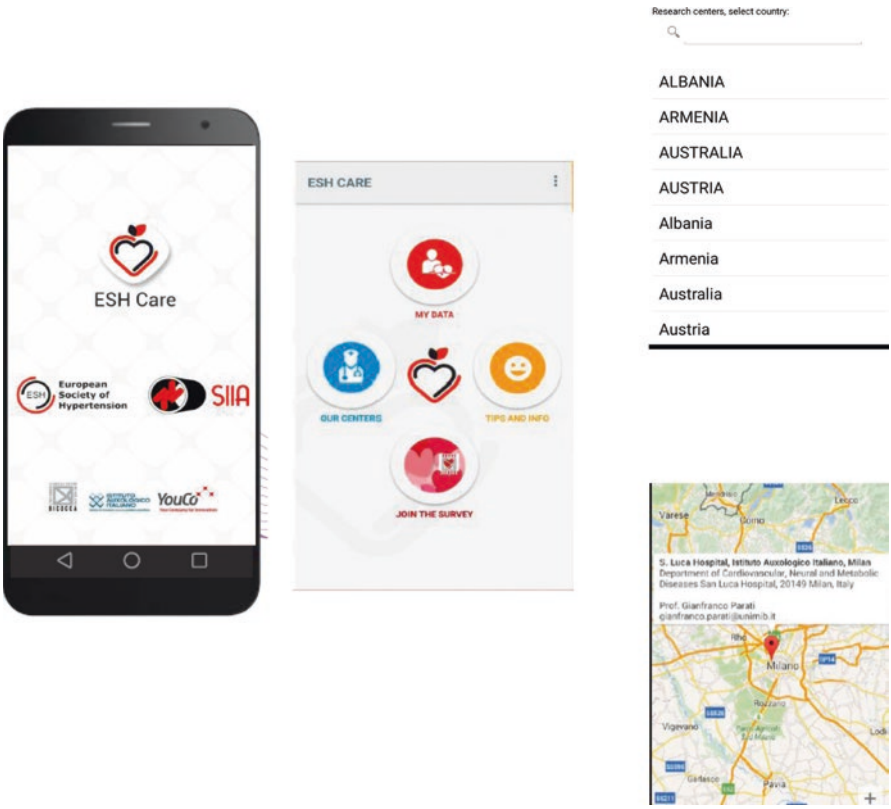


Fig. 21.2 ESH CARE App screenshots showing an index of the app content and the pages where European hypertension excellence centers can be located through "Google map" facilities

21.4 Future Perspective

More research is needed on the topic of mHealth and its contribution to increased drug adherence in hypertension. A recent consensus document by the American Heart Association (AHA) [1] suggests a few research lines to contribute to the topic, ranging from the identification of behavioural targets, individually tailored, which would be more effective in BP control, to the extrapolation of existing knowledge of effective intervention components for BP control, as derived from in-person counselling-based studies and their adaptation to mHealth platforms. Moreover, the use of delivery modalities that are currently used by individuals meets the needs of their various lifestyles and preferences. Thus, some work across mHealth platforms is encouraged (in particular, by focussing on inclusion of trials testing mHealth interventions from a broader consumer base, including elderly, disabled, etc.). Particular focus is on study techniques able to optimize a continuing patient engagement beyond 6 months, including strategies such as gamification and contingency management (incentivization). An important final point to highlight is the need of conducting trials comparing the outcome and the cost/benefit ratio of a conventional approach with those of mHealth strategies based on effective although yet possibly more costly in-person counselling interventions.

References

1. AHA statement.
2. http://apps.who.int/gb/ebwha/pdf_files/EB139/B139_8-en.pdf?ua=1.
3. World Health Organisation. mHealth—new horizons for health through mobile technologies, Global Observatory for eHealth series. Vol. 3. p. 6.
4. http://ec.europa.eu/newsroom/dae/document.cfm?doc_id=5147.
5. Mobile Technology Fact Sheet j Pew Research Center's Internet & American Life Project [Internet]. pewinternet.org. http://www.pewinternet.org/fact-sheets/mobile-technology-fact-sheet/. Accessed 31 Oct 2016.
6. Baig MM, GholamHosseini H, Connolly MJ. Mobile healthcare applications: system design review, critical issues and challenges. Australas Phys Eng Sci Med. 2015;38:23–38. https://doi.org/10.1007/s13246-014-0315-4.
7. Goldberg E, Levy P. New approaches to evaluating and monitoring blood pressure. Curr Hypertens Rep. 2016;18(6):49. https://doi.org/10.1007/s11906-016-0650-9.
8. Mobile Health 2012 j Pew Research Center's Internet & American Life Project [Internet]. pewinternet.org. http://www.pewinternet.org/2012/11/08/mobile-health-2012/. Accessed 4 Nov 2016.
9. World Health Organisation. mHealth—new horizons for health through mobile technologies, Global Observatory for eHealth series. Vol. 3.
10. Mc Kinsey and GSMA. mHealth: a new vision for healthcare. 2010.
11. Privacy and Data Management on Mobile Devices j Pew Research Center's Internet & American Life Project [Internet]. pewinternet.org. http://www.pewinternet.org/2012/09/05/privacy-and-data-management-on-mobile-devices/.
12. Kumar N, Khunger M, Gupta A, Garg N. A content analysis of smartphone–based applications for hypertension management. J Am Soc Hypertens. 2015;9(2):130–6. https://doi.org/10.1016/j.jash.2014.12.001.
13. Mobile medical applications: guidance for Food and Drug Administration Staff. 2015. http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm263366.pdf.

14. iHealth website. www.ihealthlabs.com [Internet]. http://www.ihealthlabs.com. Accessed 21 Oct 2016.
15. Withings website. http://www.withings.com/us/blood-pressure-monitor.html. Accessed 21 Oct 2016.
16. Gesche H, Grosskurth D, Küchler G, Patzak A. Continuous blood pressure measurement by using the pulse transit time: comparison to a cuff-based method. Eur J Appl Physiol. 2012;112(1):309–15. https://doi.org/10.1007/s00421-011-1983-3.
17. Bilo G, Zorzi C, Ochoa Munera JE, Torlasco C, Giuli V, Parati G. Validation of the Somnotouch-NIBP noninvasive continuous blood pressure monitor according to the European Society of Hypertension International Protocol revision 2010. Blood Press Monit. 2015;20(5):291–4. https://doi.org/10.1097/mbp.0000000000000124.
18. Plante TB, Urrea B, MacFarlane ZT, Blumenthal RS, Miller ER 3rd, Appel LJ, et al. Validation of the instant blood pressure smartphone app. JAMA Intern Med. 2016;176(5):700–2. https://doi.org/10.1001/jamainternmed.2016.0157.
19. Prados-Torres A, Poblador-Plou B, Calderón-Larrañaga A, Gimeno-Feliu LA, González-Rubio F, Poncel-Falcó A, Sicras-Mainar A, Alcalá-Nalvaiz JT. Multimorbidity patterns in primary care: interactions among chronic diseases using factor analysis. PLoS One. 2012;7:e32190. https://doi.org/10.1371/journal.pone.0032190.
20. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM, Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346:393–403. https://doi.org/10.1056/NEJMoa012512.
21. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, Hu FB, Hubbard VS, Jakicic JM, Kushner RF, Loria CM, Millen BE, Nonas CA, Pi-Sunyer FX, Stevens J, Stevens VJ, Wadden TA, Wolfe BM, Yanovski SZ. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society [published correction appears in Circulation. 2014;129(Suppl 2):S139–40]. Circulation. 2014;129(Suppl 2):S102–38. https://doi.org/10.1161/01.cir.0000437739.71477.ee.
22. Valbuena DA. Evaluating the effectiveness of an internet-based behavioral program for increasing physical activity with and without a behavioral coach. Tampa: Department of Child and Family Studies, University of South Florida; 2013.
23. Khaylis A, Yiaslas T, Bergstrom J, Gore-Felton C. A review of efficacious technology-based weight-loss interventions: five key components. Telemed J E Health. 2010;16:931–8. https://doi.org/10.1089/tmj.2010.0065.
24. Coons MJ, Demott A, Buscemi J, Duncan JM, Pellegrini CA, Steglitz J, Pictor A, Spring B. Technology interventions to curb obesity: a systematic review of the current literature. Curr Cardiovasc Risk Rep. 2012;6:120–34. https://doi.org/10.1007/s12170-012-0222-8.
25. Bacigalupo R, Cudd P, Littlewood C, Bissell P, Hawley MS, Buckley Woods H. Interventions employing mobile technology for overweight and obesity: an early systematic review of randomized controlled trials. Obes Rev. 2013;14:279–91. https://doi.org/10.1111/obr.12006.
26. A global brief on hypertension. Silent killer, global public health crisis. WHO. April 2013. WHO/DCO/WHD/2013.2.
27. Gee ME, Bienek A, Campbell NR, Bancej CM, Robitaille C, Kaczorowski J, Joffres M, Dai S, Gwadry-Sridar F, Nolan RP. Prevalence of, and barriers to, preventive lifestyle behaviors in hypertension (from a national survey of Canadians with hypertension). Am J Cardiol. 2012;109:570–5. https://doi.org/10.1016/j.amjcard.2011.09.051.
28. Nolan RP, Liu S, Shoemaker JK, Hachinski V, Lynn H, Mikulis DJ, Wennberg RA, Moy Lum-Kwong M, Zbib A. Therapeutic benefit of Internet-based lifestyle counselling for hypertension. Can J Cardiol. 2012;28:390–6. https://doi.org/10.1016/j.cjca.2012.02.012.
29. Cottrell E, Chambers R, O'Connell P. Using simple telehealth in primary care to reduce blood pressure: a service evaluation. BMJ Open. 2012;2. https://doi.org/10.1136/bmjopen-2012-001391.

30. Piette JD, Datwani H, Gaudioso S, Foster SM, Westphal J, Perry W, Rodríguez-Saldaña J, Mendoza-Avelares MO, Marinec N. Hypertension management using mobile technology and home blood pressure monitoring: results of a randomized trial in two low/middle-income countries. Telemed J E Health. 2012;18:613–20. https://doi.org/10.1089/tmj.2011.0271.
31. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, Jones DW, Materson BJ, Oparil S, Wright JT Jr, Roccella EJ, The National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003;42:1206–52. https://doi.org/10.1161/01.HYP.0000107251.49515.c2.
32. Logan AG, Irvine MJ, McIsaac WJ, Tisler A, Rossos PG, Easty A, Feig DS, Cafazzo JA. Effect of home blood pressure telemonitoring with self-care support on uncontrolled systolic hypertension in diabetics. Hypertension. 2012;60:51–7. https://doi.org/10.1161/HYPERTENSIONAHA.111.188409.
33. Kiselev AR, Gridnev VI, Shvartz VA, Posnenkova OM, Dovgalevsky PY. Active ambulatory care management supported by short message services and mobile phone technology in patients with arterial hypertension. J Am Soc Hypertens. 2012;6:346–55. https://doi.org/10.1016/j.jash.2012.08.001.
34. Magid DJ, Olson KL, Billups SJ, Wagner NM, Lyons EE, Kroner BA. A pharmacist-led, American Heart Association Heart360 Web-enabled home blood pressure monitoring program. Circ Cardiovasc Qual Outcomes. 2013;6:157–63. https://doi.org/10.1161/CIRCOUTCOMES.112.968172.
35. Liu S, Dunford SD, Leung YW, Brooks D, Thomas SG, Eysenbach G, Nolan RP. Reducing blood pressure with Internet-based interventions: a meta-analysis. Can J Cardiol. 2013;29:613–21. https://doi.org/10.1016/j.cjca.2013.02.007.
36. Parati G, Torlasco C, Omboni S, Pellegrini D. Smartphone applications for hypertension management: a potential game-changer that needs more control. Curr Hypertens Rep. 2017;19:48. https://doi.org/10.1007/s11906-017-0743-0.
37. Albini F, Liu X, Torlasco C, Soranna D, Faini A, Ciminaghi R, Celsi A, Benedetti M, Zambon A, di Rienzo M, Parati G. An ICT and mobile Health integrated approach to optimize patients' education on hypertension and its management by physicians: the Patients Optimal Strategy of Treatment(POST) pilot study. Conf Proc IEEE Eng Med Biol Soc. 2016;2016:517–20.

Part IV

Health Care Consequences of Non-adherence

Global Clinical Consequences of Poor Adherence

22

Sylvie Perreault

22.1 Global Prevalence and Healthcare Costs of Uncontrolled Hypertension

Firstly, hypertension is a chronic disease that affects over one billion people worldwide [1]. Suboptimal control of blood pressure is a major public health challenge because it is a major risk factor for major cardiovascular events [2]. It has been estimated that 7.5 million deaths per year worldwide [3–5] and about 4.58 million deaths per year in Europe are attributed to cardiovascular diseases [1, 6].

Therefore, improving blood pressure control is a major priority of clinical practice worldwide [3, 7]. Many individuals with hypertension, however, are unaware of their disorder. Among patients who are aware of their disorder, many are not treated and many are treated but their blood pressure remains poorly controlled [8]. The factors associated with the lack of treatment and control of hypertension are very complex, but may include the patient's non-adherence to prescribed drugs, patient behavioral factors, healthcare professional-related factors, and characteristics of the healthcare system [7–10].

In Europe, the blood pressure has been still persistently high [2], and this holds especially true for the general population of Europe compared with the Americans [11]. The proportions of patients with controlled hypertension in the United States approximately doubled from 27% in 1988–1994 to 52% in 2007–2010 [12, 13]. This improvement was associated with an increase in the proportion of patients using antihypertensive drugs and an improvement in blood pressure control among treated patients [12–14]. The proportion of treated patients but uncontrolled

S. Perreault, B.Pharm., Ph.D.
Faculty of Pharmacy, University of Montreal, Montreal, Quebec, Canada
e-mail: sylvie.perreault@umontreal.ca

M. Burnier (ed.), *Drug Adherence in Hypertension and Cardiovascular Protection*, Updates in Hypertension and Cardiovascular Protection,
https://doi.org/10.1007/978-3-319-76593-8_22

hypertension who were using more than three antihypertensive drugs increased from 16% in 1988–1994 to 28% in 2005–2008 [14]. Again, there is still improvement in the underlying reasons of inadequate control of hypertension in older patients, since up to 50% of them still had inadequate control [15–19]. More optimal pharmacotherapy of hypertension needs to assess if the lack of optimal control is related to the suboptimal adherence to medication or a true treatment resistant hypertension [20].

Secondly, health expenditure for cardiovascular conditions and hypertension represent a large proportion of global healthcare costs. In 2006, within Europe, the annual expenditure associated with the treatment of cardiovascular conditions was estimated to be €169 billion, 60% of which was for direct medical costs [21]. In 2012, a recent analysis of data from five European countries estimated that the direct cost of treating hypertension was €51.5 billion [22]. In 2001, the global healthcare cost related to uncontrolled hypertension in the United States was estimated to be US$378 billion, about 10% of the global healthcare expenditure [5, 23].

Non-adherence to antihypertensive drugs results in poor blood pressure control [24] and increases in healthcare use and expenditure. In 2004 in the United States, it was estimated that non-adherence to treatment increased healthcare expenditure by US$792 million [25]. It was also reported that up to 33% of drug-related admissions to hospital were due to non-adherence to prescribed drug regimens [26]. Recently, a study published in 2015 that simulated data over a 10-year period suggested that improving antihypertensive drug adherence to 70% would save approximately €332 million from a national perspective of five European countries, e.g., Italy, Germany, France, Spain, and the UK [22].

22.2 Clinical Consequences of Non-adherence to Antihypertensive Drugs

One of the most effective strategies to control blood pressure is to prescribe antihypertensive drugs, which reduce the risk of cardiovascular events, and hence decrease the economic and clinical burden of hypertension and cardiovascular disease [27–30]. However, the clinical effectiveness of antihypertensive drugs is closely linked to the patient's adherence to the prescribed treatment [31, 32].

Elevated blood pressure is associated with about 54% of cases of stroke and 47% of cases of ischemic heart disease worldwide [33]. A meta-analysis of randomized controlled trials demonstrated that the management of blood pressure among patients with hypertension is important mainly in terms of reducing the risks of cardiovascular disease and mortality [34, 35]. It is notable of a 5 mmHg of diastolic blood pressure from antihypertensive drugs compared to the pretreatment level reduced the risk of stroke by about 34% and the risk of ischemic heart disease by 21% [36].

Optimal drug adherence means that the patient takes the drugs as prescribed and continues to take the prescribed drug in accordance with the recommendations of the patient's physician, pharmacist, and health professionals [37]. In the real world,

however, the adherence to prescribed drugs is often low in patients with chronic diseases, and frequently declines in the first year after starting the drug [38–43]. Indeed, several reports have shown that nearly half of all patients who start antihypertensive drugs will stop taking their prescribed drug within 1 year [41, 44–46].

Patients with chronic diseases need a strong partnership with their physicians, pharmacists, and other healthcare professionals in order to achieve the desired long-term goals of treatment. Patients with good adherence to their antihypertensive drugs are more likely to experience the desired improvements in blood pressure, have a lower risk of adverse cardiovascular outcomes (all-cause hospitalization, cardiovascular hospitalization, cardiovascular revascularization, all-cause mortality, and cardiovascular mortality), and lower healthcare costs, compared with patients with poor adherence [27, 34, 47–53].

A meta-analysis of three decades of empirical research revealed that patients with good adherence to their antihypertensive drug had better blood pressure control than non-adherent patients to their antihypertensive therapies (odds ratio [OR]: 3.44; 95% confidence interval [CI]: 1.60–7.37) [32].

There is increasing evidence showing that patients with poor adherence to antihypertensive drugs are at much higher risk of adverse outcomes, including cardiovascular and all-cause hospitalization, than patients with good adherence [27, 53]. For instance, a cohort study showed that, among patients with low or moderate adherence, the risk of being hospitalized for cardiovascular-related diseases was increased by 33% (OR: 1.33; 95% CI: 1.25–1.41) and the risk of emergency visits by 45% (OR: 1.45; 95% CI: 1.33–1.58) compared with patients with adherence ≥80% [52]. Similarly, another cohort study revealed that a good level of adherence (>80%) to antihypertensive drugs significantly lowered the incidence of acute cardiovascular events, compared with a poor level of adherence (<40%) to antihypertensive drugs (hazard ratio [HR]: 0.62; 95% CI: 0.40–0.96) [54].

There is also evidence that the impact of non-adherence to antihypertensive agents is not only observed among patients in secondary prevention but also in primary prevention. Many observational studies based on administrative databases of patients in primary prevention reported that high adherence to antihypertensive drugs reduced the risk of cardiovascular diseases. *First*, high adherence to antihypertensive medications (≥80%) was associated with a risk reduction of 18% [RR: 0.82 (95% CI: 0.77–0.87)] of coronary artery disease compared to an adherence level of <20% [55]; *second,* high adherence (≥80%) to antihypertensive drugs significantly decreased the risk of cerebrovascular disease by 22% (rate ratio, 0.78; 95% CI, 0.70–0.87) compared to a lower level (<80%) [56]; *and thirdly,* high adherence level (≥80%) to antihypertensive therapy compared with lower adherence level (<80%) was associated with a risk reduction of chronic heart failure events (RR: 0.89; 0.80–0.99) [57]. In addition to the primary prevention, observational studies also reported significant result in secondary prevention. For instance, high adherence to antihypertensive therapy (≥80%) was mirrored by similar adherence to statins and antiplatelet agents and was associated with a lower risk of nonfatal vascular events after an ischemic stroke compared with lower adherence (>80%) (Rate Ratio 0.77 [0.70–0.86]) [58].

To date, however, few studies have investigated the impact of adherence to antihypertensive drugs on all-cause mortality or cardiovascular mortality [59]. In a cohort study using the Korean National Health Insurance Claims Databases, non-adherence to antihypertensive drugs (<80%) was associated with a significant increase in all-cause mortality and the risk of hospitalization for cardiovascular diseases (HR: 1.57; 95% CI: 1.40–1.76) [27]. The study of Kim et al., 2016 assessed the impact of adherence to antihypertensive drug on the risk of specific causes of cardiovascular-related death [60]. Among 33,728 Korean patients, 670 of them died because of ischemic heart disease or stroke during the follow-up period. Patient with poor adherence to antihypertensive drugs (<50%) were at increased risk of dying due to ischemic heart disease (HR: 1.64; 95% CI: 1.16–2.31), cerebral hemorrhage (HR: 2.19; 95% CI: 1.28–3.77), and cerebral infarction (HR: 1.92; 95% CI: 1.25–2.96) compared with patients with good adherence to antihypertensive drugs. The hazard ratios for hospitalization due to cardiovascular disease hospitalization were consistent with those for mortality.

Those results emphasize the importance of an effective management system and strategies to improve drug adherence in clinical practice. This is especially important when we consider that uncontrolled hypertension is also associated with increased risks of diabetes, stroke, atherosclerosis, and chronic kidney disease such as end stage of renal disease [61]. For instance, a high adherence level of 80% or more to antihypertensive agents compared to a lower one (<80%) was related to a risk reduction of end stage of renal disease (hazard ratio 0.67; 95% confidence intervals 0.54–0.83) [62].

They are always challenges with the estimation using real-world datasets because the impact of good adherence seems to be linked with positive clinical outcomes. But, we need to pay attention that the results of observational study designs may be biased by unmeasured residual confounding. The real-world evidence has the potential to improve efficiency across the drug development, and also the clinical usage decisions with appropriate method development for confounding such as super learning technologies. Super learning, an ensemble learning technique that can incorporate a greater number and complexity of variables, has been shown to improve outcome prediction modeling [63–65]. And also, the approach of "causal LASSO" aiming to replicate the context where treatment regimen has been randomized though unmeasured confounding that can impact the validity of the estimates, as is unavoidable in observational studies.

Technology advances and health care reform efforts are creating an opportunities to reshape the current system by which evidence generated from "Big Data" to better meet stakeholder needs but the reliability of those data needs to be considered. We can argue that validated and facile tools, based on large datasets, can help to inform at the real-time decision making to improve the clinical practice and would be invaluable but are currently limited.

22.3 Clinical Consequences of Associated Morbidities on Drug Adherence Level

Drug adherence is a complex phenomenon and may also be influenced by many factors, one of which is the coexistence of other chronic diseases [66]. On the one hand, several studies have demonstrated the protective effects of antihypertensive drugs in terms of the risks of cardiovascular morbidity and mortality [35, 67], and many patients fail to adhere to the prescribed drug, possibly due to asymptomatic and lifelong treatment of hypertension. But, on the other side, in many patients, hypertension rarely occurs in isolation. In some studies, it was noted that adherence to antihypertensive drugs was lower in patients with comorbidities [68, 69]. The existence of multiple chronic conditions is thought to reduce the likelihood of patients with hypertension adhering to the prescribed treatment [70]. It has also been noted that the presence of psychiatric conditions (e.g., depression) has adverse effects on adherence to antihypertensive drugs [66] and ultimately leads to poor blood pressure control [71].

The optimal management of common chronic cardiovascular diseases, including hypertension, coronary artery disease, and other relevant diseases such as diabetes mellitus, is important because they are among the most frequent causes of morbidity and mortality [72]. An important component of managing patients with multiple chronic diseases involves evaluating the patient's adherence to the prescribed drugs. Poor adherence weakens the effectiveness of the prescribed drugs and is related to adverse health outcomes, increased healthcare expenditure (due to hospital admissions and an excess hospital burden), impaired quality of life, and an increased mortality rate [37, 47]. In recent years, several studies of non-adherence to drugs with proven efficacy in chronically ill patients have focused specifically on various chronic diseases, especially diabetes [73–75], chronic heart failure [76–78], neurologic and psychiatric diseases [79–81], cardiovascular disease [82–86], and chronic obstructive pulmonary disease [87, 88]. And, some of those studies have also investigated the factors that may influence adherence [86, 89, 90].

In real clinical setting, patients often have complex healthcare issues due to the presence of multiple chronic diseases and interrelated health and social difficulties, and such factors may directly or indirectly interfere with healthcare priorities, self-care, behavior, and ultimately adherence [91]. A Swedish primary care study noted that the presence cardiovascular morbidity was not associated with persistence to treatment, except in patients with diabetes, who actually showed greater persistence to antihypertensive drugs [92]. Meanwhile, other studies in Germany [93] and the United States [94] found no association between the presence of associated morbidities and the persistence [93] and the adherence [94] to antihypertensive therapy. However, several coexisting diseases, such as ischemic heart disease, chronic heart failure, and dysrhythmia, were linked to higher adherence levels [54, 95].

Recently, other studies demonstrated an association between the presence of multiple comorbidities and poor adherence to cardiovascular drugs [96, 97]. In a recent cross-sectional study of approximately 113,397 adults with hypertension assigned to public health service of primary care of a south region of Spain in 2010, about one-fifth of the patients (22,952) showed poor adherence (<80%) to antihypertensive drugs [98]. The predictors of poor adherence to antihypertensive drugs were being female, younger age, rural residency, low blood pressure, polypharmacy, and the presence of mental disorders. By contrast, the presence of other cardiovascular risk factors and more frequent medical visits per year were associated with better adherence to antihypertensive drugs [98]. And, Saadat et al., 2015 reported that the proportion of patients with a high level of adherence decreased from 22% among patients with no associated comorbidities to 11% among patients with 3–5 associated comorbidities [99].

Actually, the impact of coexisting disorders on adherence to antihypertensive drugs remains unclear. The highly variable and conflicting results may be due to the type of study population, the tool used to measure adherence, the inclusion of predictors of adherence, and the number and type of comorbidities [100]. Other predictors of drug adherence such as polypharmacy, healthcare use, site of residency, and social status need also to be simultaneously considered as potential confounding factors. Moreover, none of the studies mentioned above included more than ten comorbidities, and most of them focused on cardiovascular diseases and risk factors, underestimating the impact of multiple chronic diseases.

Thus, the overall message is that the impact of coexisting disorders and polypharmacy on adherence to antihypertensive drugs or other cardiovascular therapies remains unclear. And, further research works are needed not only on the impact of associated morbidities on adherence level but also on the impact of polypharmacy on clinical outcomes, healthcare use, and its related costs. The technology advances and big data sets give the opportunity to develop appropriate methodology to assess the impact of polypharmacy on clinical outcomes and its related impact on healthcare system.

22.4 Risk Prediction of Population Impact of Implementing Guidelines and Interventions on Drug Adherence

In 2014, the Eight Joint National Committee issued revised guidelines with three important changes to the 2003 guidelines that were aimed at shifting the focus of treatment from systolic blood pressure to diastolic blood pressure in patients aged <60 years and those aged >60 years, and in patients with diabetes or chronic kidney disease [101]. Based on these changes, implementation of the 2014 guidelines would reduce the number of patients eligible for antihypertensive treatment of 1% among younger adults and of 8% in older adults [102].

The American College of Cardiology and the American Heart Association recommended cost-effectiveness evaluations should be included with the recommendations of clinical guidelines [103]. Moran et al. [104] recently applied the

competing risk Cox proportional hazard model proposed by the Framingham Heart Study to predict the clinical outcomes of patients without cardiovascular disease based on the following predictors: age, sex, diastolic and systolic blood pressure, high-density lipoprotein–cholesterol and low-density lipoprotein–cholesterol levels, the presence of chronic kidney disease, smoking status, the presence of diabetes, and the self-reported antihypertensive drug exposure. They estimated the outcomes of treating previously untreated patients aged 35–74 years over a 10-year period. The results suggest that the full implementation of the 2014 guidelines would prevent approximately 56,000 cardiovascular events and 13,000 deaths from cardiovascular causes per year, and would also provide an overall cost savings.

In addition to risk prediction based on clinical guidelines, other models, such as microsimulation, can be used to assess the population-level benefits of healthcare interventions [105]. For example, Fontil et al. [106] developed a Blood Pressure Control Model as a decision aid to assess and compare the impact of patient-level, physician-level, and system-level interventions in order to improve the clinical management of hypertension in the US population. The model combined evidence from published observational and experimental studies together with a national data survey. The Blood Pressure Control Model was also validated in two large clinical trials on the control of hypertension. The validated model was used to predict the outcomes of specific improvements, such as the frequency of medical visits, the probability of intensifying treatment according to the patient's blood pressure, and the level of drug adherence. The authors reported that a substantial improvement in blood pressure control can be achieved if there are major improvements in the care process, especially increasing the frequency of face-to-face contact. In addition, improving the physician's prescribing habits was expected to have a greater impact on blood pressure control than efforts to improve the patient's level of adherence. The proposed model can help researchers and healthcare decision-makers to invest in interventional approaches, by targeting specific approaches used in the management of particular patient populations, and to help identify methods of meeting the public health goals for managing hypertension.

Future research works and development of interventions should assess how to build drug adherence improvement intervention in longer consultations required for patients with multiples morbidities. For instance, building predictive models with electronic medical records (including filled drug claims) incorporated in real time of the consultation will allow the physicians, pharmacist, healthcare professionals, and patients to discuss in real time of the predicted risk of outcomes and the observed level of medication adherence in order to improve the clinical practice outcome and adherence to medication. At the physician level, the prediction models could have the potential to enhance decision-making on medication prescribing, target high-risk individuals, and discuss strategies to promote treatment adherence with their patients. At the patient level, we expect that the risk prediction will motivate high-risk individuals to modify their medication adherence [64, 107, 108].

22.5 Clinical Consequences of Healthcare Professional and System on Drug Adherence

In the near future, we believe that eHealth, self-monitoring, prescriber continuity, adherence among complex patients, ensuring continuity of adherence by the pharmacy, and preventive strategies (e.g., diet, healthy behavioral and physical activities) will be important components of the strategies used to help meet the public health goals for the management of hypertension. Electronic tools based on prescription refills integrated into electronic medical records may provide innovative and objective tools to measure adherence and its clinical consequence.

Moreover, the medical home visit is also intended to provide a comprehensive, patient-centered, coordinated primary care that is combined with system-based quality improvement. This model is expected to increase primary care access, improve the quality of healthcare delivery, and reduce healthcare expenditure [109–111]. The potential benefits of the medical home visit are beginning to accrue, specifically in the improvement of the quality of healthcare and reducing inappropriate healthcare interventions [112]. The emerging evidence is promising, but the inherent benefits of the medical home among persons with multiple chronic disease is still largely unknown [113]. Nevertheless, the medical home could be used to review and improve adherence in patients with multiple chronic disease [114]. In fact, better healthcare coordination could help to reduce the number of prescribers and facilitate the prescription of optimal drugs. Drug reconciliation could improve the management of the prescribed drugs by the clinicians and pharmacists, may reduce polypharmacy and drug complexity, and may ultimately improve drug adherence.

22.6 Clinical Consequences of Implementing Patient-Centered Approaches and Personalized Evaluations of Adherence to Antihypertensive Drugs

Patients with multiple comorbidities, especially cardiometabolic diseases, represent a particular challenge in clinical practice because a combination of drugs is often required to prevent and treat the diseases and their complications. A typical patient with cardiometabolic diseases may therefore require a treatment regimen composed of numerous drugs. Such patients may also require treatment for other comorbidities. Indeed, the number of elderly patients prescribed multiple drugs is rising. In 2009, 63% of patients receiving public drug insurance in six provinces in Canada claimed ≥5 classes of drugs while 23% had claims for ≥10 classes of drugs [115]. Notably, the number of classes of drugs prescribed to elderly patients increased with age: in 2009, 18% of patients aged 65–74 years, 26% of patients aged 75–84 years, and 30% of patients aged ≥85 years had claims for ≥10 drug classes.

Using multiple drugs may lead to problems such as inappropriate dosing, drug interactions, adverse drug reactions, treatment failure, and patient non adherence. The burden of drug-related morbidity in countries like Canada is enormous in terms of healthcare expenditure and avoidable morbidity and mortality [116, 117]. The

US Food and Drug Administration (FDA) and its Center for Drug Evaluation and Research estimated that the fourth leading cause of death is inappropriate use of drugs [118]. The FDA also reported that as many as 110,000 deaths per year might be due to inappropriate use of drugs. Extrapolating these estimates to Canada suggests that about 10,000 deaths per year might be related to inappropriate use of drugs, and many of these deaths could be avoided by optimizing the patients' treatment regimens. Studies, especially in the elderly, have estimated that up to 30% of hospital admissions are attributable to these unintended events [116, 117]. Several factors may explain this staggering statistic: (1) concomitant use of multiple drugs in an aging population with comorbid conditions; (2) inadvertent drug–drug interactions; and (3) high intersubject variability in the pharmacodynamic and pharmacokinetic properties of the drugs. It is well documented that the risk of drug–drug interactions increases as a function of the number of prescribed drugs: use of >5 drugs increases the risk of drug–drug interactions by four times and the use of >8 drugs increases the risk by eight times [119]. The reactions to drugs also vary between patients, and are frequently attributable to the different sequences of genes involved in the metabolism or biological effect of individual drugs. Indeed, single nucleotide polymorphisms in specific genes have been identified as major determinants of the pharmacokinetics and pharmacodynamics of drugs that are routinely administered to patients with cardiometabolic diseases, including oral antidiabetic drugs, antihypertensive drugs, statins, anticoagulants, antiplatelet drugs, and antidepressants.

The regulatory drug approval process for industry requires that in vitro and in vivo studies be conducted to test for drug–drug interactions to facilitate the prediction and prevention of these interactions. Despite the importance of drug–drug interactions to patients and industry, most in vivo and in vitro studies evaluate only one combination (two drug profiles) of potentially interacting drugs at a time. Thus, these studies cannot be generalized to patients with chronic conditions who are taking complex multidrug regimens. In addition, these studies do not consider the high intersubject variability in the pharmacodynamic effects of drugs. These limitations are very important, and new guidelines issued by the FDA recommend improvements to pharmacokinetic tests in elderly patients and in patients with multiple comorbidities.

Until recently, there was no simple way to make evidence-based predictions about the likelihood or severity of clinically important interactions in patients on multidrug regimens. The rationale for testing potential multidrug interactions is to provide clinical evidence that can support clinical decision-making in the context of risk reduction in patients on multidrug regimens [120–122]. A newly developed technology (InterMed-Rx) incorporates relevant pharmacokinetic information (bioavailability, urinary excretion, drug metabolism pathways, and drug transporters) relevant to all drugs available in Canada, and healthcare professionals to predict possible drug–drug interactions among various drugs [120]. Recent advances in molecular biology testing and genetics, as well as knowledge integration and analysis technologies, have allowed us to develop improved decision trees and algorithms to establish optimized treatment strategies, which integrate all relevant pharmacogenetic,

pharmacokinetic, and pharmacodynamic information related to individual drugs. These strategies consider genetic information, environmental factors, and the patient's unique clinical condition.

In addition to patient-centered approach and personalized evaluation, other factors need also to be discussed. Despite increasing familiarity with international guidelines, physicians do not always adhere to the guidelines and they are not always fully implemented in clinical practice [123–125]. The failure to adhere to treatment guidelines may represent a conscious decision by the physician when treating a patient. The physician's knowledge of the guidelines is also a major factor that will influence the physician's ability to adhere them [126]. This not only applies to physicians, but may also be relevant to pharmacists and other healthcare professionals who are involved in the management of patients with hypertension. It is also possible that the physician's decisions are influenced by the patient's concerns and preferences [125, 127, 128]. Clearly, comprehensive analyses of the treatment practices of physicians, pharmacists, and other healthcare professionals involved in the management of patients with hypertension (with or without associated morbidities) are needed if we hope to propose remedial and curative measures to support healthcare professionals in the management of these patients [129].

Moreover, more precise algorithms for gendered approaches may lead to a more specific and effective strategic treatment [130]. For doing so, more evidence-based clinical trial data are required, and the implementation of new gender-sensitive finding into the research and healthcare strategies is needed [130].

22.7 Clinical Consequences of Changes to Healthcare Professional- and Policy-Related Factors on Adherence

Despite the availability of clinical guidelines, clinical awareness of hypertension, and self-awareness of hypertension, the treatment and control of hypertension are far from adequate [131–134]. Some of the major challenges are the number of guidelines on this topic and the quality of these guidelines [135–138]. Al-Ansary et al. wrote a systematic review [131] on the quality, methodology, and consistency of the recommendations of several recent national clinical practice guidelines on the diagnosis, assessment, and management of hypertension. The recommendations for non-pharmacological management of hypertension were fairly consistent across the guidelines. However, the recommendations for the initial intention to treat, changes to treatment, and multidrug regimens varied among the guidelines. Moreover, important aspects of the management of drug resistance were reported in just 50% of 11 clinical practice guidelines. The variations in the methodologic quality of the guidelines suggest that their implementation may not result in worse management or better outcomes. The authors proposed that more effort is needed in order to establish a realistic approach and to be able to implement high-quality clinical practice guidelines within a national context.

One important reason why the healthcare system does not implement prevention and treatment guidelines constantly may be due to the lack of a patient-centered approach and prioritization at the point of care. We need to evaluate the time needs

to fully assess and implement all clinical relevant recommendations in order to improve their implementation [139–151]. A more systematic approach to personalizing and prioritizing guidelines may improve patient outcomes [152]. However, several studies have suggested that clinicians and healthcare professionals need to know which guidelines provide the greatest benefit to each patient, and it may be difficult to prioritize the most appropriate guideline [153–156].

In addition to implement treatment guidelines, the enforcement of outcome predictive models derived from numerical data in real time could certainly change the clinical practice model and the optimal implementation of guidelines to better organize healthcare, and improve adherence level and health-related outcomes [64, 107, 108]. We also need to fully understand the impact the implementation of predictive models in clinical practice at the patient-, physician-, pharmacist-, and healthcare professional level.

Moreover, we need to have more understanding of the role in initial medication adherence of chronic care, health system, health professionals, and patient factors that collectively influence the treatment trajectory. Patient adherence to prescribed dosing regimen is recognized as a significant challenge in the healthcare field. Objective measures of patient adherence patterns have the potential to facilitate product design to ameliorate these behaviors in real clinical setting and also to impact clinical trial design in a way that accounts for such patterns.

Strategies for the management of hypertension should continue to not only focus on preventable and modifiable risk factors but also consider the societal issues [157]. The challenge in global health practices will include challenge for health systems (governance, actors, and patients) and sustainable economic models, access to precision medicine (diagnostic strategies, precision treatment, effectiveness, and safety), health science (data access, data science, research development), new information channels (training, formation, quality of formation), and all ethical issues relevant to the challenge in global health practices (Fig. 22.1).

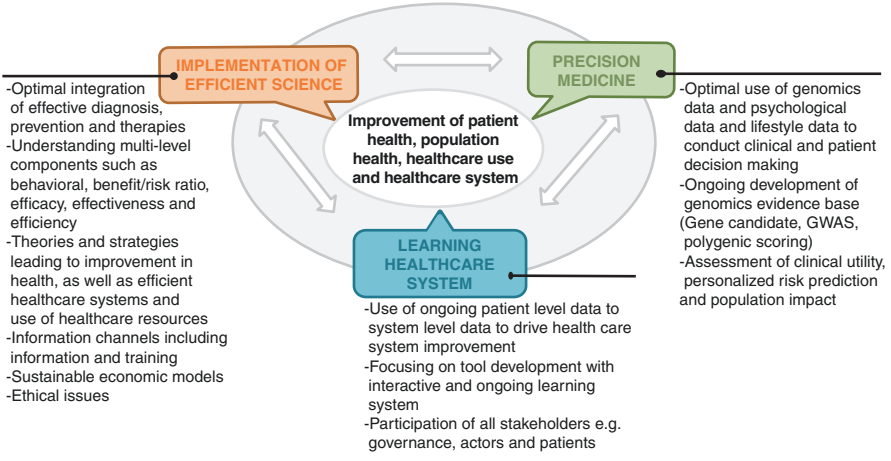


Fig. 22.1 Challenges for implementation of efficient sciences, precision medicine, health science, information channels, ethical issues, and sustainable models

References

1. World Health Organization. A global brief on hypertension. Silent killer, global public health crisis. 2016.
2. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. Lancet. 2017;389:37–55.
3. World Health Organization. Global health risks: mortality and burden of disease attributable to selected major risks. Geneva: World Health Organization; 2009. p. 1–62.
4. Heidenreich PA, et al. Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. Circulation. 2011;123:933–44.
5. Gaziano TA, Bitton A, Anand S, Weinstein MC, International Society of Hypertension. The global cost of nonoptimal blood pressure. J Hypertens. 2009;27:1472–7.
6. Townsend N, et al. Cardiovascular disease in Europe: epidemiological update 2016. Eur Heart J. 2016;37:3232–45.
7. World Health Organization. Adherence to long-term therapies: evidence for action. Geneva: World Health Organization; 2003.
8. Kearney PM, Whelton M, Reynolds K, Whelton PK, He J. Worldwide prevalence of hypertension: a systematic review. J Hypertens. 2004;22:11–9.
9. Lewanczuk R. Innovations in primary care: implication for hypertension detection and treatment. Can J Cardiol. 2006;22:614–6.
10. Gee ME, et al. Antihypertensive medication use, adherence, stops, and starts in Canadians with hypertension. Can J Cardiol. 2012;28:383–9.
11. Wolf-Maier K, et al. Hypertension prevalence and blood pressure levels in 6 European countries, Canada, and the United States. JAMA. 2003;289:2363–9.
12. Egan BM, Zhao Y, Axon RN. US trends in prevalence, awareness, treatment, and control of hypertension, 1988-2008. JAMA. 2010;303:2043–50.
13. Egan BM, Zhao Y. Different definitions of prevalent hypertension impact: the clinical epidemiology of hypertension and attainment of Healthy People goals. J Clin Hypertens (Greenwich). 2013;15:154–61.
14. Egan BM, Zhao Y, Axon RN, Brzezinski WA, Ferdinand KC. Uncontrolled and apparent treatment resistant hypertension in the United States, 1988 to 2008. Circulation. 2011;124:1046–58.
15. Resnick HE, Shorr RI, Kuller L, Franse L, Harris TB. Prevalence and clinical implications of American Diabetes Association-defined diabetes and other categories of glucose dysregulation in older adults: the health, aging and body composition study. J Clin Epidemiol. 2001;54:869–76.
16. Smith NL, et al. Glucose, blood pressure, and lipid control in older people with and without diabetes mellitus: the Cardiovascular Health Study. J Am Geriatr Soc. 2002;50:416–23.
17. de Rekeneire N, et al. Racial differences in glycemic control in a well-functioning older diabetic population: findings from the Health, Aging and Body Composition Study. Diabetes Care. 2003;26:1986–92.
18. Ostchega Y, Dillon CF, Hughes JP, Carroll M, Yoon S. Trends in hypertension prevalence, awareness, treatment, and control in older U.S. adults: data from the National Health and Nutrition Examination Survey 1988 to 2004. J Am Geriatr Soc. 2007;55:1056–65.
19. Robinson JG, Booth B. Statin use and lipid levels in older adults: National Health and Nutrition Examination Survey, 2001 to 2006. J Clin Lipidol. 2010;4:483–90.
20. Egan BM, et al. Prevalence of optimal treatment regimens in patients with apparent treatment-resistant hypertension based on office blood pressure in a community-based practice network. Hypertension. 2013;62:691–7.
21. Leal J, Luengo-Fernandez R, Gray A, Petersen S, Rayner M. Economic burden of cardiovascular diseases in the enlarged European Union. Eur Heart J. 2006;27:1610–9.
22. Mennini FS, et al. Cost of poor adherence to anti-hypertensive therapy in five European countries. Eur J Health Econ. 2015;16:65–72.

23. Lim SS, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380:2224–60.
24. Breekveldt-Postma NS, et al. Effect of persistent use of antihypertensives on blood pressure goal attainment. Curr Med Res Opin. 2008;24:1025–31.
25. LaFleur J, Oderda GM. Methods to measure patient compliance with medication regimens. J Pain Palliat Care Pharmacother. 2004;18:81–7.
26. McDonnell PJ, Jacobs MR. Hospital admissions resulting from preventable adverse drug reactions. Ann Pharmacother. 2002;36:1331–6.
27. Shin S, et al. Effect of antihypertensive medication adherence on hospitalization for cardiovascular disease and mortality in hypertensive patients. Hypertens Res. 2013;36:1000–5.
28. Ong KL, Cheung BM, Man YB, Lau CP, Lam KS. Prevalence, awareness, treatment, and control of hypertension among United States adults 1999-2004. Hypertension. 2007;49:69–75.
29. Krousel-Wood MA, Muntner P, He J, Whelton PK. Primary prevention of essential hypertension. Med Clin North Am. 2004;88:223–38.
30. Chobanian AV, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA. 2003;289:2560–72.
31. Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. J Clin Hypertens (Greenwich). 2008;10:348–54.
32. DiMatteo MR, Giordani PJ, Lepper HS, Croghan TW. Patient adherence and medical treatment outcomes: a meta-analysis. Med Care. 2002;40:794–811.
33. Lawes CM, Vander Hoorn S, Rodgers A, International Society of Hypertension. Global burden of blood-pressure-related disease, 2001. Lancet. 2008;371:1513–8.
34. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009;338:b1665.
35. Blood Pressure Lowering Treatment Trialists' Collaboration, et al. Effects of different regimens to lower blood pressure on major cardiovascular events in older and younger adults: meta-analysis of randomised trials. BMJ. 2008;336:1121–3.
36. Law M, Wald N, Morris J. Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy. Health Technol Assess. 2003;7:1–94.
37. Osterberg L, Blaschke T. Adherence to medication. N Engl J Med. 2005;353:487–97.
38. Burke TA, et al. Discontinuation of antihypertensive drugs among newly diagnosed hypertensive patients in UK general practice. J Hypertens. 2006;24:1193–200.
39. Benner JS, et al. Long-term persistence in use of statin therapy in elderly patients. JAMA. 2002;288:455–61.
40. Perreault S, et al. Persistence and determinants of statin therapy among middle-aged patients free of cardiovascular disease. Eur J Clin Pharmacol. 2005;61:667–74.
41. Perreault S, et al. Persistence with treatment in newly treated middle-aged patients with essential hypertension. Ann Pharmacother. 2005;39:1401–8.
42. Perreault S, et al. Persistence and determinants of statin therapy among middle-aged patients for primary and secondary prevention. Br J Clin Pharmacol. 2005;59:564–73.
43. Simard P, et al. Persistence and adherence to oral antidiabetics: a population-based cohort study. Acta Diabetol. 2015;52:547–56.
44. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. BMJ. 2008;336:1114–7.
45. Mazzaglia G, et al. Patterns of persistence with antihypertensive medications in newly diagnosed hypertensive patients in Italy: a retrospective cohort study in primary care. J Hypertens. 2005;23:2093–100.
46. Sung SK, et al. First-year treatment adherence among outpatients initiating antihypertensive medication in Korea: results of a retrospective claims review. Clin Ther. 2009;31:1309–20.
47. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. Med Care. 2005;43:521–30.

48. Liu L, et al. Blood pressure reduction for the secondary prevention of stroke: a Chinese trial and a systematic review of the literature. Hypertens Res. 2009;32:1032–40.
49. Ho PM, et al. Medication nonadherence is associated with a broad range of adverse outcomes in patients with coronary artery disease. Am Heart J. 2008;155:772–9.
50. Cramer JA, Benedict A, Muszbek N, Keskinaslan A, Khan ZM. The significance of compliance and persistence in the treatment of diabetes, hypertension and dyslipidaemia: a review. Int J Clin Pract. 2008;62:76–87.
51. Dragomir A, et al. Impact of adherence to antihypertensive agents on clinical outcomes and hospitalization costs. Med Care. 2010;48:418–25.
52. Pittman DG, Tao Z, Chen W, Stettin GD. Antihypertensive medication adherence and subsequent healthcare utilization and costs. Am J Manag Care. 2010;16:568–76.
53. Wu PH, et al. Relationship of blood pressure control and hospitalization risk to medication adherence among patients with hypertension in Taiwan. Am J Hypertens. 2010;23:155–60.
54. Mazzaglia G, et al. Adherence to antihypertensive medications and cardiovascular morbidity among newly diagnosed hypertensive patients. Circulation. 2009;120:1598–605.
55. Perreault S, et al. Adherence level of antihypertensive agents in coronary artery disease. Br J Clin Pharmacol. 2010;69:74–84.
56. Kettani FZ, et al. Impact of a better adherence to antihypertensive agents on cerebrovascular disease for primary prevention. Stroke. 2009;40:213–20.
57. Perreault S, et al. Better adherence to antihypertensive agents and risk reduction of chronic heart failure. J Intern Med. 2009;266:207–18.
58. Perreault S, et al. Adherence to antihypertensive agents after ischemic stroke and risk of cardiovascular outcomes. Neurology. 2012;79:2037–43.
59. Wong MC, et al. Drug adherence and the incidence of coronary heart disease- and stroke-specific mortality among 218,047 patients newly prescribed an antihypertensive medication: a five-year cohort study. Int J Cardiol. 2013;168:928–33.
60. Kim S, et al. Medication adherence and the risk of cardiovascular mortality and hospitalization among patients with newly prescribed antihypertensive medications. Hypertension. 2016;67:506–12.
61. Schafer HH, Scheunert U. Costs of current antihypertensive therapy in Switzerland: an economic evaluation of 3,489 patients in primary care. Swiss Med Wkly. 2013;143:w13854.
62. Roy L, et al. Adherence to antihypertensive agents improves risk reduction of end-stage renal disease. Kidney Int. 2013;84:570–7.
63. van der Laan MJ, Polley EC, Hubbard AE. Super learner. Stat Appl Genet Mol Biol. 2007;6:Article25.
64. Obermeyer Z, Emanuel EJ. Predicting the future—big data, machine learning, and clinical medicine. N Engl J Med. 2016;375:1216–9.
65. Kennedy EH, Ma Z, McHugh MD, Small DS. Nonparametric methods for doubly robust estimation of continuous treatment effects. J R Stat Soc Ser B. 2017;79(4):1229–45.
66. Krousel-Wood M, et al. Association of depression with antihypertensive medication adherence in older adults: cross-sectional and longitudinal findings from CoSMO. Ann Behav Med. 2010;40:248–57.
67. ESH/ESC Task Force for the Management of Arterial Hypertension. 2013 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC): ESH/ESC Task Force for the Management of Arterial Hypertension. J Hypertens. 2013;31:1925–38.
68. Ghembaza MA, Senoussaoui Y, Tani MK, Meguenni K. Impact of patient knowledge of hypertension complications on adherence to antihypertensive therapy. Curr Hypertens Rev. 2014;10:41–8.
69. An J, Nichol MB. Multiple medication adherence and its effect on clinical outcomes among patients with comorbid type 2 diabetes and hypertension. Med Care. 2013;51:879–87.
70. Carretero OA, Oparil S. Essential hypertension: part II: treatment. Circulation. 2000;101:446–53.

71. Scalco AZ, Scalco MZ, Azul JB, Lotufo Neto F. Hypertension and depression. Clinics (Sao Paulo). 2005;60:241–50.
72. Munger MA, Van Tassell BW, LaFleur J. Medication nonadherence: an unrecognized cardiovascular risk factor. MedGenMed. 2007;9:58.
73. Jamous RM, et al. Adherence and satisfaction with oral hypoglycemic medications: a pilot study in Palestine. Int J Clin Pharm. 2011;33:942–8.
74. Ahmad NS, Ramli A, Islahudin F, Paraidathathu T. Medication adherence in patients with type 2 diabetes mellitus treated at primary health clinics in Malaysia. Patient Prefer Adherence. 2013;7:525–30.
75. Simard P, et al. Impact of adherence to oral antidiabetics on all-cause mortality: a population based study. Value Health. 2015;18:A611.
76. Dunlay SM, Eveleth JM, Shah ND, McNallan SM, Roger VL. Medication adherence among community-dwelling patients with heart failure. Mayo Clin Proc. 2011;86:273–81.
77. Wu JR, Lennie TA, Dekker RL, Biddle MJ, Moser DK. Medication adherence, depressive symptoms, and cardiac event-free survival in patients with heart failure. J Card Fail. 2013;19:317–24.
78. Perreault S, et al. Older adults with heart failure treated with carvedilol, bisoprolol, or metoprolol tartrate: risk of mortality. Pharmacoepidemiol Drug Saf. 2017;26:81–90.
79. Dibonaventura M, Gabriel S, Dupclay L, Gupta S, Kim E. A patient perspective of the impact of medication side effects on adherence: results of a cross-sectional nationwide survey of patients with schizophrenia. BMC Psychiatry. 2012;12:20.
80. Sweileh WM, et al. Self-reported medication adherence and treatment satisfaction in patients with epilepsy. Epilepsy Behav. 2011;21:301–5.
81. De las Cuevas C, Penate W, Sanz EJ. Risk factors for non-adherence to antidepressant treatment in patients with mood disorders. Eur J Clin Pharmacol. 2014;70:89–98.
82. Cooper DC, et al. Antidepressant adherence and risk of coronary artery disease hospitalizations in older and younger adults with depression. J Am Geriatr Soc. 2014;62:1238–45.
83. Hashmi SK, et al. Factors associated with adherence to anti-hypertensive treatment in Pakistan. PLoS One. 2007;2:e280.
84. Li WW, Kuo CT, Hwang SL, Hsu HT. Factors related to medication non-adherence for patients with hypertension in Taiwan. J Clin Nurs. 2012;21:1816–24.
85. Holt E, et al. Sex differences in barriers to antihypertensive medication adherence: findings from the cohort study of medication adherence among older adults. J Am Geriatr Soc. 2013;61:558–64.
86. Wang W, Lau Y, Loo A, Chow A, Thompson DR. Medication adherence and its associated factors among Chinese community-dwelling older adults with hypertension. Heart Lung. 2014;43:278–83.
87. Agh T, Inotai A, Meszaros A. Factors associated with medication adherence in patients with chronic obstructive pulmonary disease. Respiration. 2011;82:328–34.
88. Blais L, Forget A, Ramachandran S. Relative effectiveness of budesonide/formoterol and fluticasone propionate/salmeterol in a 1-year, population-based, matched cohort study of patients with chronic obstructive pulmonary disease (COPD): effect on COPD-related exacerbations, emergency department visits and hospitalizations, medication utilization, and treatment adherence. Clin Ther. 2010;32:1320–8.
89. Jansa M, et al. Multidimensional analysis of treatment adherence in patients with multiple chronic conditions. A cross-sectional study in a tertiary hospital. Patient Educ Couns. 2010;81:161–8.
90. Tsai KT, et al. Medication adherence among geriatric outpatients prescribed multiple medications. Am J Geriatr Pharmacother. 2012;10:61–8.
91. Tinetti ME, Bogardus ST Jr, Agostini JV. Potential pitfalls of disease-specific guidelines for patients with multiple conditions. N Engl J Med. 2004;351:2870–4.
92. Qvarnstrom M, et al. Persistence to antihypertensive drug treatment in Swedish primary healthcare. Eur J Clin Pharmacol. 2013;69:1955–64.

93. Hasford J, Schroder-Bernhardi D, Rottenkolber M, Kostev K, Dietlein G. Persistence with antihypertensive treatments: results of a 3-year follow-up cohort study. Eur J Clin Pharmacol. 2007;63:1055–61.
94. Morris AB, et al. Factors associated with drug adherence and blood pressure control in patients with hypertension. Pharmacotherapy. 2006;26:483–92.
95. Chapman RH, Petrilla AA, Benner JS, Schwartz JS, Tang SS. Predictors of adherence to concomitant antihypertensive and lipid-lowering medications in older adults: a retrospective, cohort study. Drugs Aging. 2008;25:885–92.
96. Wong MC, et al. The association between multimorbidity and poor adherence with cardiovascular medications. Int J Cardiol. 2014;177:477–82.
97. Wong MC, et al. Factors associated with multimorbidity and its link with poor blood pressure control among 223,286 hypertensive patients. Int J Cardiol. 2014;177:202–8.
98. Calderon-Larranaga A, et al. Non-adherence to antihypertensive medication: the role of mental and physical comorbidity. Int J Cardiol. 2016;207:310–6.
99. Saadat Z, et al. Adherence to antihypertensives in patients with comorbid condition. Nephrourol Mon. 2015;7:e29863.
100. Stewart M, Fortin M, Britt HC, Harrison CM, Maddocks HL. Comparisons of multi-morbidity in family practice—issues and biases. Fam Pract. 2013;30:473–80.
101. James PA, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311:507–20.
102. Navar-Boggan AM, Pencina MJ, Williams K, Sniderman AD, Peterson ED. Proportion of US adults potentially affected by the 2014 hypertension guideline. JAMA. 2014;311:1424–9.
103. Anderson JL, et al. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. Circulation. 2014;129:2329–45.
104. Moran AE, et al. Cost-effectiveness of hypertension therapy according to 2014 guidelines. N Engl J Med. 2015;372:447–55.
105. Abraham JM. Using microsimulation models to inform U.S. health policy making. Health Serv Res. 2013;48:686–95.
106. Fontil V, et al. Simulating strategies for improving control of hypertension among patients with usual source of Care in the United States: the blood pressure control model. J Gen Intern Med. 2015;30:1147–55.
107. Jha AK. Learning from the past to improve VA health care. JAMA. 2016;315:560–1.
108. Rumsfeld JS, Joynt KE, Maddox TM. Big data analytics to improve cardiovascular care: promise and challenges. Nat Rev Cardiol. 2016;13:350–9.
109. Hussey PS, Eibner C, Ridgely MS, McGlynn EA. Controlling U.S. health care spending—separating promising from unpromising approaches. N Engl J Med. 2009;361:2109–11.
110. Fields D, Leshen E, Patel K. Analysis & commentary. Driving quality gains and cost savings through adoption of medical homes. Health Aff (Millwood). 2010;29:819–26.
111. Rosenthal MB, et al. Will the patient-centered medical home improve efficiency and reduce costs of care? A measurement and research agenda. Med Care Res Rev. 2010;67:476–84.
112. Peikes D, Zutshi A, Genevro JL, Parchman ML, Meyers DS. Early evaluations of the medical home: building on a promising start. Am J Manag Care. 2012;18:105–16.
113. Sidorov JE. The patient-centered medical home for chronic illness: is it ready for prime time? Health Aff (Millwood). 2008;27:1231–4.
114. Beadles CA, et al. Do medical homes increase medication adherence for persons with multiple chronic conditions? Med Care. 2015;53:168–76.
115. https://secure.cihi.ca/free_products/HCIC_2011_seniors_report_en.pdf. 2011.
116. Committee on Quality of Health Care in America, Institute of Medicine. To err is human: building a safer health system. Washington, DC: National Academies Press; 2000.
117. Baker GR, et al. The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada. CMAJ. 2004;170:1678–86.

118. Center for Drug Evaluation And Research (CDER), FDA. http://www.Fda.Gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm110632.Htm#adrs: Prevalence and incidence.
119. Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA. Drug-drug interactions among elderly patients hospitalized for drug toxicity. JAMA. 2003;289:1652–8.
120. Turgeon J, Michaud V. Clinical decision support systems: great promises for better management of patients' drug therapy. Expert Opin Drug Metab Toxicol. 2016;12:993–5.
121. Zakrzewski-Jakubiak H, et al. Detection and prevention of drug-drug interactions in the hospitalized elderly: utility of new cytochrome p450-based software. Am J Geriatr Pharmacother. 2011;9:461–70.
122. Doan J, Zakrzewski-Jakubiak H, Roy J, Turgeon J, Tannenbaum C. Prevalence and risk of potential cytochrome P450-mediated drug-drug interactions in older hospitalized patients with polypharmacy. Ann Pharmacother. 2013;47:324–32.
123. Wang L. Physician-related barriers to hypertension management. Med Princ Pract. 2004;13:282–5.
124. Mehta SS, Wilcox CS, Schulman KA. Treatment of hypertension in patients with comorbidities: results from the study of hypertensive prescribing practices (SHyPP). Am J Hypertens. 1999;12:333–40.
125. Hyman DJ, Pavlik VN. Self-reported hypertension treatment practices among primary care physicians: blood pressure thresholds, drug choices, and the role of guidelines and evidence-based medicine. Arch Intern Med. 2000;160:2281–6.
126. Milchak JL, Carter BL, James PA, Ardery G. Measuring adherence to practice guidelines for the management of hypertension: an evaluation of the literature. Hypertension. 2004;44:602–8.
127. McAlister FA, O'Connor AM, Wells G, Grover SA, Laupacis A. When should hypertension be treated? The different perspectives of Canadian family physicians and patients. CMAJ. 2000;163:403–8.
128. Hyman DJ, Pavlik VN. Characteristics of patients with uncontrolled hypertension in the United States. N Engl J Med. 2001;345:479–86.
129. Ragot S, Beneteau M, Guillou-Bonnici F, Herpin D. Prevalence and management of hypertensive patients in clinical practice: cross-sectional registry in five countries outside the European Union. Blood Press. 2016;25:104–16.
130. EUGenMed Cardiovascular Clinical Study Group, et al. Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes. Eur Heart J. 2016;37:24–34.
131. Al-Ansary LA, et al. A systematic review of recent clinical practice guidelines on the diagnosis, assessment and management of hypertension. PLoS One. 2013;8:e53744.
132. Cai L, Liu A, Zhang L, Li S, Wang P. Prevalence, awareness, treatment, and control of hypertension among adults in Beijing, China. Clin Exp Hypertens. 2012;34:45–52.
133. Whelton PK, He J, Muntner P. Prevalence, awareness, treatment and control of hypertension in North America, North Africa and Asia. J Hum Hypertens. 2004;18:545–51.
134. Alsuwaida A, Alghonaim M. Gender disparities in the awareness and control of hypertension. Clin Exp Hypertens. 2011;33:354–7.
135. Wang YR, Alexander GC, Stafford RS. Outpatient hypertension treatment, treatment intensification, and control in Western Europe and the United States. Arch Intern Med. 2007;167:141–7.
136. Fervers B, et al. Predictors of high quality clinical practice guidelines: examples in oncology. Int J Qual Health Care. 2005;17:123–32.
137. Watine J, et al. Conflict between guideline methodologic quality and recommendation validity: a potential problem for practitioners. Clin Chem. 2006;52:65–72.
138. Nagy E, et al. Do guidelines for the diagnosis and monitoring of diabetes mellitus fulfill the criteria of evidence-based guideline development? Clin Chem. 2008;54:1872–82.
139. Tai-Seale M, McGuire TG, Zhang W. Time allocation in primary care office visits. Health Serv Res. 2007;42:1871–94.
140. Yarnall KS, Pollak KI, Ostbye T, Krause KM, Michener JL. Primary care: is there enough time for prevention? Am J Public Health. 2003;93:635–41.

141. Maciosek MV, et al. Priorities among effective clinical preventive services: results of a systematic review and analysis. Am J Prev Med. 2006;31:52–61.
142. Ostbye T, et al. Is there time for management of patients with chronic diseases in primary care? Ann Fam Med. 2005;3:209–14.
143. Flocke SA, Frank SH, Wenger DA. Addressing multiple problems in the family practice office visit. J Fam Pract. 2001;50:211–6.
144. Fiscella K, Epstein RM. So much to do, so little time: care for the socially disadvantaged and the 15-minute visit. Arch Intern Med. 2008;168:1843–52.
145. Pimlott N. Preventive care: so many recommendations, so little time. CMAJ. 2005;173:1345–6.
146. Tarn DM, et al. How much time does it take to prescribe a new medication? Patient Educ Couns. 2008;72:311–9.
147. Hadley J, Mitchell JM, Sulmasy DP, Bloche MG. Perceived financial incentives, HMO market penetration, and physicians' practice styles and satisfaction. Health Serv Res. 1999;34:307–21.
148. Nutting PA, Rost K, Smith J, Werner JJ, Elliot C. Competing demands from physical problems: effect on initiating and completing depression care over 6 months. Arch Fam Med. 2000;9:1059–64.
149. Linzer M, et al. Managed care, time pressure, and physician job satisfaction: results from the physician worklife study. J Gen Intern Med. 2000;15:441–50.
150. Mechanic D. Physician discontent: challenges and opportunities. JAMA. 2003;290:941–6.
151. Nutting PA, et al. Competing demands in the office visit: what influences mammography recommendations? J Am Board Fam Pract. 2001;14:352–61.
152. Taksler GB, Keshner M, Fagerlin A, Hajizadeh N, Braithwaite RS. Personalized estimates of benefit from preventive care guidelines: a proof of concept. Ann Intern Med. 2013;159:161–8.
153. Piette JD, Kerr EA. The impact of comorbid chronic conditions on diabetes care. Diabetes Care. 2006;29:725–31.
154. O'Connor PJ. Setting evidence-based priorities for diabetes care improvement. Int J Qual Health Care. 2003;15:283–5.
155. Braithwaite RS, Concato J, Chang CC, Roberts MS, Justice AC. A framework for tailoring clinical guidelines to comorbidity at the point of care. Arch Intern Med. 2007;167:2361–5.
156. Walter LC, Bertenthal D, Lindquist K, Konety BR. PSA screening among elderly men with limited life expectancies. JAMA. 2006;296:2336–42.
157. Melgarejo JD, et al. Prevalence, treatment, and control rates of conventional and ambulatory hypertension across 10 populations in 3 continents. Hypertension. 2017;70:50–8.