

## REVIEW ARTICLE

# Factors associated with antihypertensive medication non-adherence: a systematic review

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Non-adherence to antihypertensive medication is the most important cause of uncontrolled blood pressure and is influenced by multiple interrelating factors. Understanding the complexity of medication non-adherence and its associated factors is important to determine intervention strategies. Therefore, a systematic review was performed aimed to identify factors associated with antihypertensive medication non-adherence. Different databases were searched for observational studies reporting on factors associated with non-adherence to antihypertensive medication. Titles, abstracts and full texts were reviewed by three researchers. Subsequently, the methodological quality of each study was assessed. Factors that were extracted from the included studies were categorised as factors with consistent or inconsistent evidence to put their potential importance into perspective. Forty-four studies were included. Higher co-payment, side effects and a poor patient–provider relationship were identified as factors with consistent evidence since consistent significant relationships were found for these factors whenever studied. The relationships between non-adherence and multiple other factors were inconsistent among the reviewed studies. However, some of these factors deserve some consideration. Since multiple potentially relevant factors were identified, patient-tailored interventions focussing on identifying and addressing patients' specific barriers to adherence are needed. Further research should clarify the influence of inconsistent factors on adherence and their potential to be addressed in interventions.

*Journal of Human Hypertension* (2017) 31, 687–694; doi:10.1038/jhh.2017.48; published online 29 June 2017

## INTRODUCTION

Hypertension contributes to the burden of cardiovascular disease and premature morbidity and mortality.<sup>1</sup> The ability of pharmacological treatment of hypertension to reduce the risk of cardiovascular events and decrease morbidity and mortality is well established.<sup>2,3</sup> However, due to poor adherence to antihypertensive medication, optimal clinical outcomes are not achieved.<sup>4,5</sup>

Medication adherence is defined as the process by which patients take their medication as agreed upon with their prescriber.<sup>6</sup> The World Health Organisation (WHO) estimates the prevalence of non-adherence to antihypertensive medication between 30 and 50%. This variation relates to the differences in drug class, type of prevention and methods used to measure adherence.<sup>2,7</sup> Adherence to medication is influenced by multiple interrelating factors. The WHO introduced a framework to classify factors that influence adherence into five dimensions: patient-related factors, for example, inadequate beliefs or skills, social/economic-related factors, for example, poor health literacy or low social support, condition-related factors, for example, presence of comorbidities, therapy-related factors, for example, complex drug regimen and health system/health-care team-related factors, for example, insufficient communication with health-care provider.<sup>2</sup>

A number of reviews have been published concerning the variables associated with cardiovascular medication non-adherence-related topics. Bowry *et al.* evaluated the predictors of non-adherence to cardiovascular medication and concentrated on resource-limited settings.<sup>8</sup> Lemstra and Alsabbagh<sup>9</sup> performed

a meta-analysis of database and cohort studies providing estimates of risk indicators associated with non-adherence to antihypertensive medication assessed with objective measures. A systematic review by AlGhurair *et al.*<sup>10</sup> examined patients' adherence barriers to antihypertensive medication, and aimed to determine which adherence barriers were assessed in self-report measures. In sum, the study populations, settings and methods of these reviews differed with respect to this review. Especially, by means of categorising factors according to consistent and inconsistent evidence, a thorough overview was provided in this review. To our knowledge, this unique method has not been performed in antihypertensive medication research as yet.

A comprehensive understanding of the complex character of antihypertensive medication non-adherence and its associated factors is necessary to develop intervention strategies aimed at the improvement of medication adherence. Therefore, the present systematic review aims to identify factors associated with antihypertensive medication non-adherence.

## METHODS

### Data source and search strategy

In the present systematic review the PRISMA statement for reporting systematic reviews has been followed.<sup>11</sup> MEDLINE, EMBASE, PsycINFO and The Cochrane Library were searched up from January 1990 to July 2016 to identify English-language research articles of observational studies reporting on factors

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Received 15 March 2017; revised 15 May 2017; accepted 25 May 2017; published online 29 June 2017

**Table 1.** Inclusion criteria for study selection

Inclusion criteria	
Quantitative, observational (retrospective, cross-sectional, prospective) studies aiming to investigate the association of factors with medication non-adherence	
Study participants of $\geq 18$ years old; living in a Western country <sup>a</sup> ;	
having hypertension and using antihypertensive medication	
Medication non-adherence is the primary outcome of the study, and is assessed by means of refill data of pharmacy databases and/or validated self-reported questionnaires	
Studies performing multivariable statistical analysis methods to determine the association of factors with non-adherence	

<sup>a</sup>Statistics Netherlands defines a Western country as a country in Europe (excluding Turkey), North America, Oceania, Indonesia or Japan.

associated with medication non-adherence. The search terms related to medication adherence were agreed upon and tested by two authors (DMvdL, JGH) (Supplementary Appendix 1). It was decided to use broader search terms to prevent missing eligible articles. The search for articles was performed by one of the authors (DMvdL) supported by an experienced librarian.

**Study selection**

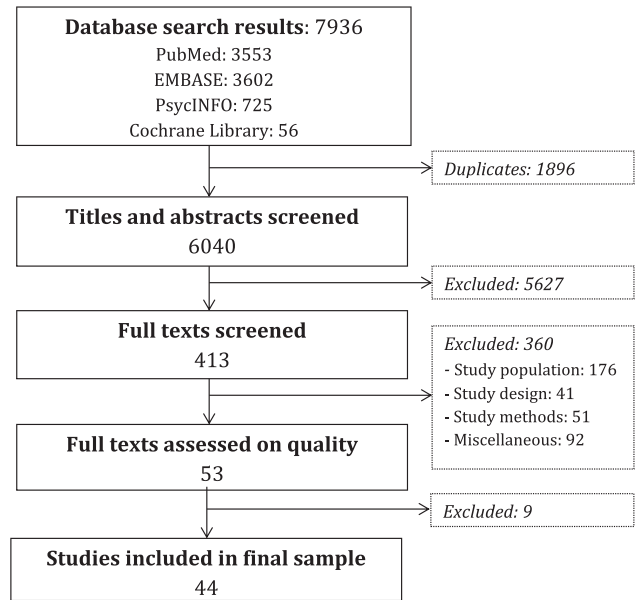
A small number of titles and abstracts were screened and preliminary discussed to reach agreement on interpretations, definitions and inclusion criteria. Studies were selected in three steps. In step one, two authors (DMvdL, JGH) independently scanned titles and abstracts to identify articles corresponding with the pre-defined inclusion criteria (Table 1). In step two, full-text papers of relevant articles were retrieved and reviewed for inclusion in the review by three authors (DMvdL, JGH or DMvdL, PJME). In step three, the methodological quality of eligible full-text articles was independently evaluated by the same three authors. Prior to quality assessment a small number of articles were reviewed in order to reach homogenous quality assessment. Disagreement regarding eligibility of articles was discussed until consensus was reached.

**Methodological quality assessment**

The methodological quality assessment was based on the Quality Assessment Tool for quantitative studies developed by the Effective Public Health Practice Project.<sup>12</sup> Since certain domains were not applicable to this review, including blinding and intervention integrity-related questions, the tool was adapted to the needs of the present study. The following five domains were evaluated: selection bias, confounders, data collection methods, withdrawals and drop-outs, and analysis. A sub score of weak, moderate or strong was given for each domain. Studies with two or more weak scores were excluded from this review.

**Data extraction**

Data were extracted by one investigator (DMvdL.) into a data extraction form. Information regarding first author, country, research aim, study design, participants, measurement and definition of the outcome was extracted. Subsequently, factors that were examined on the association with (non-)adherence were extracted from each study. Factors were categorised as factors with consistent or inconsistent evidence. Factors with consistent evidence have consistent significant relationships with medication non-adherence whenever studied. Factors with inconsistent evidence have both significant and non-significant relationships with medication non-adherence and/or have no conclusive relationships, since both positive and negative associations were found. Factors were excluded when studied by less than three studies or when factors were medication class-, country-, policy- or health system-specific.



**Figure 1.** Flow diagram of the inclusion procedure.

**RESULTS**

**Selection of the studies**

The database search resulted in 7936 articles of which 1896 duplicate articles were excluded (Figure 1). The titles and abstracts of 6040 articles were reviewed according to the inclusion criteria leaving 413 articles. The full-text papers of these articles were retrieved and reviewed for inclusion which resulted in a total of 53 studies eligible for the methodological quality assessment. After excluding nine studies with a weak quality score, 44 studies were included in the final sample.

**Characteristics of the included studies**

An overview of the study characteristics is presented in Table 2. Most studies ( $n=35$ ) were conducted in the USA.<sup>13-47</sup> In 22 studies refill data from pharmacy databases were used to calculate non-adherence.<sup>13-16,21,25,32,33,35,37,39-45,48-52</sup> The Medication Possession Ratio ( $n=10$ ) was the measure most used.<sup>14,21,25,33,39,40,42,43,48,49</sup> In general, this method is used to calculate the time a patient has medication available and is reported as a percentage. All studies defined a score below 80% as non-adherence. In 21 studies self-report questionnaires were used to assess non-adherence,<sup>17-20,22,24,26-31,34,36,38,46,47,53-56</sup> of which two used two different questionnaires.<sup>34,55</sup> The four-item Morisky Medication Adherence Scale was the questionnaire most used ( $n=12$ ).<sup>18,19,22,24,27-30,34,36,55,56</sup> One study used both refill data and self-report data.<sup>23</sup> In studies using self-report questionnaires the sample size was relatively small (range 71-2595). In contrast, the sample size of studies using pharmacy refill databases was

**Table 2.** Overview of characteristics of the included studies (N = 44)

Author	Country	Research aim	Study design	Participants (N) mean age $\pm$ s.d.	Measurement of non-adherence	Definition of non-adherence
Adams <i>et al.</i> <sup>13</sup>	USA	To identify potential modifiable health system determinants of medication use	Retrospective study	Patients with hypertension newly on AH therapy (44 167) mean age NR	Pharmacy database calculating the PDC	Non-adherence is < 80%
Baggarty <i>et al.</i> <sup>14</sup>	USA	To test the association of drug classes, race, gender, age and comorbidity with adherence	Retrospective study	Patients with hypertension using antihypertensive medication (4544) mean age NR	Pharmacy database calculating the MPR	Non-adherence is < 0.8
Bailey <i>et al.</i> <sup>15</sup>	USA	To determine the most important patient and health-care factors associated with non-adherence	Cross-sectional study	Patients with hypertension using AH medication (49 479) 48.5 $\pm$ 9.6 years	Pharmacy database calculating Medication Refill Adherence	Non-adherence is < 80%
Bailey <i>et al.</i> <sup>16</sup>	USA	To determine risk factors for failure to obtain timely medication refills	Retrospective study	Patients with hypertension using AH medication (1366) mean age NR	Pharmacy databases	Non-compliance is the frequency of refill failure
Calderon-Larrañaga <i>et al.</i> <sup>48</sup>	Spain	To analyse the association between mental and physical comorbidity and non-adherence	Cross-sectional study	Patients with hypertension using AH medication (113 397) 70.5 $\pm$ 11.6 years	Pharmacy database calculating the MPR	Non-adherence is < 80%
Crowley <i>et al.</i> <sup>17</sup>	USA	To identify risk factors associated with non-adherence to self-management behaviour (i.e. proper medication use)	Cross-sectional study	Patients with hypertension using AH medication (636) 61.0 $\pm$ 12.0 years	Self-reported Medication-Taking Scale questionnaire	Non-adherence is a score $\leq$ 2
Cuffee <i>et al.</i> <sup>18</sup>	USA	To examine the association between happiness and medication adherence among African Americans	Cross-sectional study	African American patients with hypertension using AH medication (573) 53.6 $\pm$ 9.7 years	MMAS questionnaire with four items	Lower scores indicate worse adherence
Cuffee <i>et al.</i> <sup>19</sup>	USA	To determine the proportion of the relationship between medication adherence and discrimination	Cross-sectional study	African American patients diagnosed with hypertension using AH medication (780) 53.7 $\pm$ 9.9 years	MMAS questionnaire with four items	Lower scores indicate worse adherence
Forsyth <i>et al.</i> <sup>20</sup>	USA	To examine the relationship between perceived discrimination and medication adherence	Prospective study	Black patients with hypertension using AH medication (463) 57.9 $\pm$ 11.8 years	MMAS questionnaire with four items	Higher scores indicate greater non-adherence
Gentil <i>et al.</i> <sup>49</sup>	Canada	To identify the determinants of AH medication adherence	Prospective study	Patients with hypertension using AH medication (926) mean age NR	Database calculating the MPR	Not further specified
Hedna <i>et al.</i> <sup>50</sup>	Sweden	To identify factors associated with non-adherence	Retrospective study	Patients with hypertension using AH medication (867) 66.0 $\pm$ 12.1 years	Pharmacy database calculating the PDC	Non-adherence is < 80%
Holmes <i>et al.</i> <sup>21</sup>	USA	To determine patient factors associated with medication adherence	Retrospective study	Patients with hypertension using AH medication (168 522) 76.1 years	Pharmacy database calculating the MPR	Non-adherence is MPR < 80%
Holt <i>et al.</i> <sup>23</sup>	USA	To examine the association between health-related quality of life and medication adherence	Cross-sectional study	Patients with hypertension using AH medication (2180) 75.0 $\pm$ 5.6 years	(1) MMAS questionnaire with eight items and (2) database calculating MPR	(1) low adherence is a score < 6 and (2) non-adherence is MPR < 0.8
Holt <i>et al.</i> <sup>22</sup>	USA	To determine whether sociodemographic, clinical, health-care system, psychological, and behavioural factors are associated with adherence	Cross-sectional study	Patients with hypertension using AH medication (2194) 75.0 $\pm$ 5.5 years	MMAS questionnaire with eight items	Poor adherence is MMAS score < 6
Hyre <i>et al.</i> <sup>24</sup>	USA	To determine the factors associated with poor AH medication adherence	Cross-sectional study	Patients with hypertension using AH medication (295) 55.8 years	MMAS questionnaire with eight items	Poor adherence is MMAS score < 6
Ishisaka <i>et al.</i> <sup>25</sup>	USA	To understand race/ethnicity as a factor related to medication-taking behaviour	Retrospective study	Patients with hypertension using AH medication (51 722) mean age NR	Pharmacy database calculating the MPR	Non-adherence is MPR < 0.80
Kim <i>et al.</i> <sup>26</sup>	USA	To examine predictors of intentional and unintentional non-adherence	Cross-sectional study	Korean American patients with hypertension using AH medication (208) 52.6 $\pm$ 5.6 years	Hill-Bone Compliance Scale (medication intake subscale) with four items	Higher scores indicate lower adherence
Kivimäki <i>et al.</i> <sup>51</sup>	Finland	To examine whether retirement is associated with changes in adherence	Cohort study	Patients with hypertension using AH medication (3468) mean age NR	Pharmacy database calculating the PDC	Poor adherence is PDC < 40%
Kressin <i>et al.</i> <sup>27</sup>	USA	To examine the links between patient race, experiences with clinicians, attitudes and beliefs and adherence	Cross-sectional study	Patients with hypertension using AH medication (793) mean age NR	MMAS questionnaire and additional items	Non-adherence is yes to at least one item
Krousel-Wood <i>et al.</i> <sup>28</sup>	USA	To evaluate the associations between depressive symptoms, social support and medication adherence	Cross-sectional and prospective study	Patients with hypertension using AH medication (2180) 75.1 $\pm$ 5.6 years	MMAS questionnaire with eight items	Low adherence is MMAS score < 6
Krousel-Wood <i>et al.</i> <sup>29</sup>	USA	To assess the association between risk factors and medication adherence	Prospective study	Patients with hypertension using AH medication (1965) 75.0 $\pm$ 5.6 years	MMAS questionnaire with eight items	Decline in adherence is a decrease in MMAS score of $\geq$ 2 points
Lewis <i>et al.</i> <sup>30</sup>	USA	To determine patient, provider and health-care system factors associated with adherence	Cross-sectional study	Black male patients with hypertension using AH medication (252) 56.6 $\pm$ 11.6 years	MMAS questionnaire with four items	Higher scores indicate greater non-adherence

**Table 2. (Continued)**

Author	Country	Research aim	Study design	Participants (N) mean age ± s.d.	Measurement of non-adherence	Definition of non-adherence
Li et al. <sup>31</sup>	USA	To examine the association of cultural factors with medication adherence	Cross-sectional study	Chinese immigrant patients with hypertension using AH medication (200) 70.6 ± 10.3 years	MMAS questionnaire modified to AH medication	Non-adherence is MMAS < 80%
Lötsch et al. <sup>53</sup>	Austria	To evaluate causes for non-adherence	Cross-sectional study	Patients with hypertension using AH medication (323) mean age NR	MMAS questionnaire with four items	Non-adherence is yes to at least one item
Lowry et al. <sup>46</sup>	USA	To examine associations between patient characteristics and non-adherence	Cross-sectional study	Patients with hypertension using AH medication (588) 63.4 ± 11.4 years	MMAS questionnaire with four items	Non-adherence is yes to at least one item
Maciejewski et al. <sup>32</sup>	USA	To examine the impact of medication copayment increase on adherence	Retrospective study	Patients with hypertension using AH medication (7090) mean age NR	Pharmacy database calculating the PDC	Non-adherence is PDC < 80%
Maquire et al. <sup>54</sup>	Ireland	To explore the impact of depressive symptoms and medication beliefs on medication adherence	Cross-sectional study	Patients with hypertension using AH medication (326) mean age NR	Reported Adherence to Medications scale questionnaire	Non-adherence is < 80%
Morris et al. <sup>33</sup>	USA	To examine the association between patient characteristics and medication adherence	Cross-sectional study	Patients with hypertension using AH medication (469) 56.6 ± 10.8 years	Pharmacy database calculating the MPR	Non-adherence is MPR < 80%
Morrison et al. <sup>55</sup>	Multi-national	To identify determinants of patient non-adherence	Cross-sectional study	Patients with hypertension using AH medication (2395) mean age NR	(1) MMAS with four items and (2) MARS with five items	(1) non-adherence is yes to ≥ 1 item and (2) lower scores indicate low adherence
Nabi et al. <sup>52</sup>	Finland	To examine the importance of sense of coherence, optimism, pessimism, hostility, anxiety with regard to adherence	Cohort study	Patients with hypertension using AH medication (1021) mean age NR	Pharmacy database calculating the therapeutic coverage with DDD	Non-adherence is zero days of therapeutic coverage
Natarajan et al. <sup>56</sup>	Canada	To identify factors associated with adherence	Cross-sectional study	Patients with hypertension using AH medication (527) 66.0 ± 10.0 years	MMAS questionnaire with four items	Non-adherence is yes to at least one item
Phillips et al. <sup>34</sup>	USA	To measure treatment-related beliefs, habits and coherence in beliefs in predicting adherence	Prospective study	Patients with hypertension using AH medication (71) 67.9 ± 12.3 years	(1) MMAS with eight items and (2) MARS with five items	(1) lower scores and (2) higher scores indicate worse adherence
Ren et al. <sup>35</sup>	USA	To identify patient and prescriber characteristics influencing compliance	Cross-sectional study	Patients with hypertension using AH medication (1292) 65.2 ± 10.3 years	Pharmacy database	Non-compliance is < 0.8
Richardson et al. <sup>36</sup>	USA	To examine associations between discrimination and adherence in African Americans	Cross-sectional study	African American patients with hypertension using AH medication (780) 53.7 ± 9.9 years	MMAS questionnaire with four items	Higher scores indicate worse adherence
Roumie et al. <sup>37</sup>	USA	To evaluate patient-centred primary care as a determinant of medication adherence	Prospective study	Patients with hypertension using AH medication (499) 66.8 ± 11.1 years	Pharmacy database calculating the days medication is available	Non-adherence is < 0.8
Schoenthaler et al. <sup>38</sup>	USA	To evaluate effects of patients' perceptions of their providers' communication on adherence	Cross-sectional study	African American patients with hypertension using AH medication (439) 57.7 ± 12.1 years	MMAS questionnaire with four items	Lower scores indicate worse adherence
Shaya et al. <sup>39</sup>	USA	To identify predictors of compliance with AH therapy	Retrospective study	Patients with hypertension using AH medication (568) 50.0 ± 9.7 years	Pharmacy database calculating the MPR	Non-compliance is MPR < 80%
Siegel et al. <sup>40</sup>	USA	To study factors associated with medication adherence	Cross-sectional study	Patients with hypertension using AH medication (40 492) 68.6 ± 11.2 years	Pharmacy database calculating the MPR	Non-adherence is MPR < 80%
Steiner et al. <sup>41</sup>	USA	To develop prediction rules for AH medication adherence	Retrospective study	Patients with hypertension using AH medication (111 473) mean age NR	Pharmacy database on filling prescriptions	Non-adherence is < 80%
Taira et al. <sup>43</sup>	USA	To measure the impact of medication co-payment on compliance with AH medication	Retrospective study	Patients with hypertension using AH medication (114 232) 64.0 ± 14.0 years	Pharmacy database calculating the MPR	Non-compliance is MPR < 0.8
Taira et al. <sup>42</sup>	USA	To identify predictors of adherence for specific groups, particularly Asian Americans	Cross-sectional study	Asian Pacific American patients with hypertension using AH medication (28 395) 63.1 ± 13.4 years	Database calculating the MPR	Non-adherence is MPR < 0.8
Trivedi et al. <sup>47</sup>	USA	To examine whether emotional well-being and marital status are related to adherence	Cross-sectional study	Patients with hypertension using AH medication (636) 61.3 ± 12.3 years	MMAS questionnaire with four items	Non-adherence is yes to at least one item
Wang et al. <sup>44</sup>	USA	To identify factors associated with poor adherence, including behavioural characteristics	Cross-sectional study	Patients with hypertension using AH medication (496) mean age NR	Database calculating the PDC	Non-compliance is PDC < 80%
Xie et al. <sup>45</sup>	USA	To compare adherence with single-, double-, and triple-pill treatment	Retrospective study	Patients with hypertension using AH medication (17 465) mean age NR	Pharmacy database calculating the PDC	Non-adherence is < 80%

Abbreviations: AH, antihypertensive; DDD, defined daily doses; MARS, medication adherence report scale; MMAS, Morisky medication adherence scale; MPR, medication possession ratio; NA, not applicable; NR, not reported; PDC, proportion of days covered.

much larger (range 469–168 522). The mean age of participants in almost all studies was >50 years.

Factors consistently associated with medication non-adherence  
Factors were listed according to the WHO multidimensional adherence model into patient-, social/economic-, condition-, therapy- and health-care team-related factors (Table 3).<sup>2</sup>

Higher co-payment, side effects and a poor patient–provider relationship were whenever studied consistently associated with antihypertensive medication non-adherence. *Higher co-payment* was identified in three studies using a retrospective study design.<sup>13,32,43</sup> These studies included a significant sample of patients and used pharmacy refill data to measure medication adherence. Co-payment was defined as higher levels of fixed amounts that patients were obliged to pay for their medication<sup>13,43</sup> or a recent increase of co-payment for medication.<sup>32</sup> Based on the methodological quality assessment two of these studies were rated as moderate<sup>32,43</sup> and one study as strong.<sup>13</sup> Discomfort caused by *side effects* was identified in four cross-sectional studies using self-report questionnaires to assess medication adherence and which were assessed as moderate<sup>22,26</sup> or strong<sup>46,47</sup> based upon the methodological quality assessment tool. Three studies found that having more side effects was associated with non-adherence,<sup>26,46,47</sup> whereas one study identified a specific antihypertensive side effect as important predictor, namely reduced sexual functioning in males.<sup>22</sup> In the three studies, the number of side effects was assessed by means of administering a list of common antihypertensive side effects, including dry mouth, itching, tiredness, dizziness or sexual problems. A *poor patient–provider relationship* was identified in four studies assessed with moderate<sup>19,24,37</sup> or strong methodological quality.<sup>35</sup> Two studies using self-report questionnaires to assess medication adherence found the following poor relationship-related aspects: less trust in the physician,<sup>19</sup> being uncomfortable about asking questions to the doctor, wanting to spend more time with the doctor and not seeing the primary doctor when needed.<sup>24</sup> Two other studies using pharmacy refill data to assess medication adherence found that patients perceiving less involvement in treatment decision<sup>35</sup> and perceiving poor patient-centred primary care<sup>37</sup> were more likely to be non-adherent.

Factors inconsistently associated with medication non-adherence  
For the following factors both significant and non-significant relationships were reported: high body mass index, low concerns about the illness or potential adverse effects of medication, poor hypertension knowledge, low self-efficacy, discrimination, male gender, younger age, racial/ethnic minority status, marital status, low education level, employment, low income, insecure financial status, number of co-morbidities, having diabetes, depression, history of cardiovascular disease, duration of hypertension, complex medication regime, multiple dosing regimen, fewer health-care provider visits, specialised health-care use and dissatisfaction with the communication of health-care providers. For the factors male gender, number of comorbidities and complex medication regime no conclusive relationship with antihypertensive medication non-adherence could be established, since they showed to have both positive and negative relationships with adherence.

## DISCUSSION

The present systematic review included 44 studies with an overall moderate to strong methodological quality. Among the multiple factors that were found to be associated with non-adherence, only higher co-payment, side effects and a poor patient–provider relationship appeared to be factors with consistent evidence.

The consistent relationship between higher co-payment and antihypertensive medication non-adherence has also been found in reviews on adherence to cardiovascular medication<sup>8</sup> and statin therapy.<sup>57</sup> These out-of-pocket expenses of patients provide a barrier to medication adherence. Health-care providers should ask patients about possible medication cost-related problems. They should also inform patients about possible medication options and the co-payment levels associated with each, in order to make cost-effective decisions. Appropriate treatment adjustments can be made to minimize costs. Strategies that can contribute to minimizing costs include the use of generic drugs and fixed-dose combination forms. However, it should be noted that co-payment related issues depend on the type of health insurance system, and therefore might be less relevant in some countries.

Side effects appeared to be a consistent factor of antihypertensive medication non-adherence. In two other reviews similar results were found.<sup>8,58</sup> The discomfort of patients due to the presence of medication side effects can also be a reason to discontinue therapy. Health-care providers should monitor the occurrence and progression of side effects and change the medication regime if needed. They should also be conscious of the transition in which patients' concerns about the side effects exceeds their beliefs in the necessity of the medication.

A poor patient–provider relationship was also identified as a consistent factor of antihypertensive medication non-adherence. Aspects of a poor patient–provider relationship as described in the studies included were less trust in the physician, being uncomfortable about asking questions, not seeing the primary doctor when needed, perceived less involvement in treatment decisions and poor perceived patient-centred care. Another systematic review on barriers to medication adherence among elderly also identified a poor patient–provider relationship as a barrier to adherence.<sup>58</sup> Health-care providers should make an effort to improve the patient–provider relationship, by creating an open and trustworthy atmosphere and by ensuring patient-centred care in which patients are involved in treatment decisions.

A number of other factors showed to have inconsistent relationships with antihypertensive medication non-adherence. Although findings were inconsistent, certain factors should be considered since the majority of the studies that examined these factors showed significant relationships with medication non-adherence. These factors include: low self-efficacy, discrimination, racial/ethnic minority status, marital status, depression, history of cardiovascular disease, multiple dosing regimen, fewer health-care provider visits, specialised health-care use and dissatisfaction with the communication of health-care providers. Some of these factors could be used as identifiers for patients at risk for antihypertensive medication non-adherence. Other factors are modifiable and may be used as potential targets for intervention strategies. Further research is needed to clarify the influence of these factors on medication non-adherence, for instance by examining the variety in study populations and settings, with respect to age, drug class and disease severity.

## Strengths and limitations

A strength of the present systematic review is its categorising character. An overview of the factors that have been examined in the included studies was provided. By means of this method, factors were categorised as factors with consistent and inconsistent evidence. To our knowledge this method has not been previously used in antihypertensive medication research.

Some limitations need to be discussed. A meta-analysis is the best approach to report pooled effects of factors associated with non-adherence. However, this could not be accomplished because of the heterogeneity of the included studies particularly with respect to the use of different adherence measurement methods, and rather differing study populations and settings. Therefore, it

**Table 3.** Factors associated with antihypertensive medication non-adherence in the included studies

Factors	Number of studies with a factor associated with non-adherence	Number of studies with a factor associated with adherence	Number of studies with a factor with a non-significant association
<i>Patient-related</i>			
Body Mass Index, high	2 <sup>15,22</sup>	-	3 <sup>13,17,36</sup>
Beliefs, low concerns	2 <sup>31,55</sup>	-	2 <sup>17,54</sup>
Hypertension knowledge, poor	1 <sup>26</sup>	-	2 <sup>17,24</sup>
Self-efficacy, low	5 <sup>27,30,36,53,55</sup>	-	2 <sup>26,54</sup>
Discrimination, racial/weight-based	3 <sup>19,20,36</sup>	-	1 <sup>30</sup>
<i>Social/economic-related</i>			
Gender, male	6 <sup>15,24,29,47,49,55</sup>	3 <sup>19,43,48</sup>	16 <sup>13-18,21,25,26,36,38,40,42,50,54,56</sup>
Age, younger	21 <sup>13,15,16,19,25,30,33,35,36,38-43,48,50,53-56</sup>	-	11 <sup>14,17,18,21,24,26,29,31,37,47,49</sup>
Racial/ethnic minority status	16 <sup>13-15,17,21,24,25,33,39-43,46-48</sup>	-	3 <sup>26,35,37</sup>
Marital status, unmarried	4 <sup>29,33,41,47</sup>	-	2 <sup>26,49</sup>
Education level, low	4 <sup>17,19,42,46</sup>	-	11 <sup>18,24,26,29,35-38,49,50,56</sup>
Employment	1 <sup>55</sup>	-	2 <sup>17,53</sup>
Income, low	3 <sup>19,49,50</sup>	-	7 <sup>13,21,24,26,30,36,38</sup>
Co-payment, higher <sup>a</sup>	3 <sup>13,32,43</sup>	-	-
Financial status, insecure	3 <sup>17,22,55</sup>	-	2 <sup>18,46</sup>
<i>Condition-related</i>			
Comorbidities, more	5 <sup>14,21,39,42,43</sup>	3 <sup>15,25,48</sup>	7 <sup>26,29,30,38,49,50,53</sup>
Having diabetes	-	4 <sup>15,41,42,46</sup>	4 <sup>13,17,24,40</sup>
Having depression	13 <sup>15,20,22,23,28-30,38,40,41,44,48,49</sup>	-	5 <sup>13,17,26,33,54</sup>
History of CVD	2 <sup>24,42</sup>	-	1 <sup>13</sup>
Duration of hypertension	2 <sup>24,37</sup>	-	2 <sup>26,56</sup>
<i>Therapy-related</i>			
Side effects <sup>a</sup>	4 <sup>22,26,46,47</sup>	-	-
Medication regimen, complex	6 <sup>14,21,41,45,48,49</sup>	6 <sup>15,35,40,50,55,56</sup>	2 <sup>16,53</sup>
Dosing regimen, multiple	3 <sup>16,39,55</sup>	-	1 <sup>53</sup>
<i>Health-care system-related</i>			
Health-care provider visits, fewer	3 <sup>15,16,48</sup>	-	1 <sup>13</sup>
Health-care use, specialised	3 <sup>35,42,48</sup>	-	1 <sup>50</sup>
Dissatisfaction with communication	2 <sup>22,38</sup>	-	1 <sup>30</sup>
Patient-provider relationship, poor <sup>a</sup>	4 <sup>19,24,35,37</sup>	-	-

Abbreviation: CVD, cardiovascular disease. <sup>a</sup>Factors with consistent evidence, since exclusively consistent relationships were found whenever studied.

was decided to categorise the examined factors based on the consistency of the findings. Another limitation concerns the main objective of some included studies, that is, to investigate the correlation of a specific factor with non-adherence adjusting for different covariates. In these studies results on the significance of these covariates were not always reported. Furthermore, it was decided to exempt factors that were examined by less than three studies. As a consequence, some potentially interesting factors may have not been reviewed, for instance habit strength and health literacy. These factors were only examined by one study. Another limitation might be the exclusion of studies with a weak methodological quality. However, to ensure that important factors were not missed, the factors that were examined in these studies were evaluated. No additional important factors were identified. At last, the majority of the included studies were conducted in the USA. Nevertheless, due to the exemption of country-, policy- or health system-specific factors during data

extraction and in view of the rather generic character of the identified factors, eventual bias of study results may be considered very limited.

The findings of the present systematic review underline the need for the development of interventions targeted to specific subpopulation or interventions tailored to patients' specific intake barriers, such as higher co-payment and side effects. Furthermore, patient-provider relationships should be improved by increasing trust, collaboration and patients' involvement in decision making. Although for some provider-related factors inconsistent findings were observed in the present review, certain factors, for example, dissatisfaction with communication, deserve some consideration when developing interventions, for instance by providing communication skills training to health-care providers. Further research is needed in which the influence of inconsistent factors on adherence and their potential to be addressed in interventions can be clarified.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## ACKNOWLEDGEMENTS

The authors thank the Royal Dutch Pharmacists Association for financial support and medical librarian Rene Otten for supporting the development of the search strategy and database search. This work was financially supported by the Royal Dutch Pharmacists Association.

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