Chapter 1
Definitions of Resistant Hypertension and Epidemiology of Resistant Hypertension

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Introduction

Hypertension has long been known to be a significant cardiovascular risk factor [1] and remains one of the most preventable causes of premature, especially cardiovascular and renal, morbidity and mortality in both developed and developing countries [2, 3]. Hypertension accounts for, or contributes to, 62% of all strokes and 49% of all cases of heart disease responsible for 7.1 million deaths per year: approximately 13% of total world deaths [2].

Antihypertensive trials consistently demonstrate a significant risk reduction benefit from lowering blood pressure. A reduction of 5 mmHg in diastolic pressure over 5 years is associated with a 42% relative reduction in stroke and a 14% relative reduction in the risk of an ischemic heart disease event [4]. At the start of the millennium, the estimated number of adults with hypertension worldwide was 972 million, with that number expected to rise to 1.56 billion by 2025 [2].

Blood pressure is a continuous variable that is normally distributed [5, 6]. There is no natural "cutoff" above which hypertension definitely exists and one below which it definitely does not. Indeed, the risk of stroke and ischemic heart disease events is continuously associated with blood pressure [7], with no evidence of a threshold value down to at least 115/75 mmHg [5]. Above 115/70 mmHg, the risk of cardiovascular disease doubles for every 20/10 mmHg rise in BP across all the blood pressure ranges for both men and women [5]. Therefore, in the absence of a distinct cutoff value to define hypertension, the threshold blood pressure determining the presence of hypertension is generally defined as the level of blood pressure above which antihypertensive treatment has been shown to reduce the development

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or progression of disease [8]. Most societies and guidelines recommend lowering blood pressure to below 140/90 mmHg [8–13] with some suggesting higher thresholds for the elderly [8, 9, 12] and lower thresholds for those at higher high risk including patients with diabetic mellitus and patients with chronic kidney disease (Table 1.1) [8, 9, 12].

Table 1.1 Guideline comparisons of target blood pressure and definitions of resistant hypertension

	Population	Target blood pressure, mmHg	Definition of resistant hypertension
Report from the panel members of the Eighth Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 2014 [10]	General ≥60 years	<150/90	Not specifically defined but no differences highlighted from the Seventh Report of the Joint National Committee (see below)
	General <60 years	<140/90	
	Diabetes mellitus	<140/90	
	Chronic kidney disease	<140/90	
The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 2003 [6]	General	<140/90	"Resistant hypertension is defined as the failure to achieve goal BP in patients who are adhering to full doses of an appropriate 3-drug regimen that includes a diuretic"
	Diabetes mellitus	<130/90	
	Chronic kidney disease	<130/90	
American Heart Association/International Society of Hypertension Clinical Practice Guidelines for the management of hypertension in the community [9]	General <80	<140/90	"Blood pressure >140/90 mmHg despite using 3 agents in full or maximally tolerated doses"
	General ≥80 years	<150/90	
	Chronic kidney disease with albuminuria	<130/80	
European Society of Hypertension/European Society of Cardiology guidelines for the management of arterial hypertension 2013 [12]	General nonelderly	<140/90	"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 blood pressure to <140/90 mmHg"
	General elderly <80 years	<150/90	
	General elderly ≥80 years	<150/90	
	Diabetes mellitus	<140/85	
	Chronic kidney disease: no proteinuria	<140/90	
	Chronic kidney disease with proteinuria	<130/90	

(continued)

Table 1.1 (continued)

	Population	Target blood pressure, mmHg	Definition of resistant hypertension
Kidney Disease: Improving Global Outcomes Blood Pressure Work Group 2012 [13]	Chronic kidney disease: no proteinuria	≤140/90	Not defined
	Chronic kidney disease with proteinuria	≤130/80	
National Institute for Health and Clinical Excellence guideline: clinical management of primary hypertension in adults 2011 [8]	General <80 years	<140/90	"Blood pressure not controlled to <140/90 mmHg despite optimal or best tolerated doses of 3rd line treatment"
	General ≥80 years	<150/90	

Most hypertension can be treated and controlled with lifestyle changes and antihypertensive agents [14]. However, there remains a significant subgroup of the hypertensive population that does not achieve optimal control of blood pressure despite adequate hypertension treatment and lifestyle changes [15–19]. The reasons for this are complex and often poorly understood. However, these patients remain at very high cardiovascular and renal risk. It is, therefore, important to use consistent definitions and terminology to accurately characterize these patients, identify risk factors, and elucidate investigation and treatment strategies.

The Term "Resistant Hypertension"

The term *resistant hypertension* appears to have been first used in 1960 [20]. Interestingly, this article examined the effects of iproniazid, an antituberculous agent with antidepressant properties, which had incidentally been observed to lower blood pressure. Twenty hypertensive patients were "carefully selected" and all had a blood pressure of over 200/100 mmHg despite treatment. All had electrocardiographic evidence of hypertensive heart disease and all had hypertensive retinopathy. In this article, the term "intractable" also appears to have been used interchangeably with "resistant" to describe hypertension. The term "refractory hypertension," probably first used in 1958 [21], has also been used interchangeably with "resistant hypertension." Interestingly, patients with refractory hypertension were "defined" in this article as those who had "shown a lack of hypotensive response and an absence of significant symptomatic improvement with various drug therapies." The mean blood pressure in these patients was 236/121 mmHg—eye-watering figures! It is worth remembering, however, that in 1958 these therapies appear to have been limited to drugs such as reserpine [22, 23], hydralazine [24], and autonomic blocking agents including ecolid [25]. No wonder the major cause of therapeutic failure was an intolerance of the antihypertensive agents' side effects.

With an increasing understanding of the critical importance of treating hypertension and blood pressure control, the development of treatment guidelines, and the increasing availability of well-tolerated antihypertensive agents, the need for a clear definition of resistant hypertension became increasingly apparent.

Definitions of Resistant Hypertension

If you cannot measure it you cannot improve it. (Lord Kelvin 1824–1907)

At the most basic level, resistant hypertension can be defined as difficult to control blood pressure in a hypertensive patient. It is not severe hypertension [26]. As with the definition of hypertension itself, any definition of resistant hypertension is to some extent arbitrary. However, any definition also serves to identify patients who might benefit from further investigation or specialist treatment. Indeed, this has been the prime motivator for most efforts to arrive at a workable definition. Several attempts have been made to produce a definition of resistant hypertension that can be consistently applied (Table 1.1).

In 2003, the Seventh Report of the Joint National Committee 7 (JNC7) defined resistant hypertension as "the failure to achieve goal blood pressure in patients who are adhering to full doses of an appropriate 3-drug regimen that includes a diuretic" [6]. Goal blood pressure was defined as less than 140/90 mmHg or less than 130/80 mmHg in patients with diabetes mellitus or chronic kidney disease [6].

In 2008, the American Heart Association further refined the definition of resistant hypertension as "blood pressure that remains above goal in spite of the concurrent use of 3 antihypertensive agents of different classes. Ideally, one of the agents should be a diuretic and all agents should be prescribed at optimal dose amounts" [27]. This definition also includes patients "whose blood pressure is controlled with use of more than 3 medications. That is, patients whose blood pressure is controlled but require 4 or more medications to so should be considered resistant to treatment" [27]. Although an improvement, there remain several ambiguities even in this definition including: "goal" blood pressure is inconsistent across conditions and guidelines; the need for a diuretic to be one of the treatments is not mandatory; and the term "optimal dose amounts" can be considered subjective. Nevertheless, most studies on resistant hypertension since have used different interpretations of this definition [28].

In its recent joint guidelines document, the European Society of Cardiology and European Society of Hypertension further attempted to define resistant hypertension: "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 systolic and diastolic blood pressure values to less than 140/90 mmHg" [12].

Although not specifically part of the definition, most guidelines recommend the exclusion of apparent or pseudo-resistant hypertension, that is, inadequate blood

pressure control in a patient receiving appropriate treatment who does not actually have resistant hypertension. Most often, pseudo-resistance arises from (i) poor clinic blood pressure measurement technique, (ii) the "white coat" effect, (iii) poor patient adherence to prescribed treatment, or (iv) a "suboptimal" antihypertensive regime [29]. Pseudohypertension, or the presence of heavily calcified arteriosclerotic arteries that are poorly compressible giving rise to cuff-related artifact, should also be eliminated before a diagnosis of resistant hypertension is made [29].

Other terms that are being used in the literature include refractory hypertension and controlled resistant hypertension. Refractory hypertension has been defined to include patients who meet the definition but whose blood pressure *IS NOT* controlled on maximally tolerated doses of four or more antihypertensive agents [30]. Controlled resistant hypertension patients are patients who meet the criteria for resistant hypertension but whose blood pressure *IS* controlled on maximal tolerated doses of four or more medications [30]. Although, again arbitrary, these definitions may help to subclassify patients for further investigation or treatment. Perhaps more importantly, they add more clarity when studies reporting findings on resistant hypertension present their results and allow for easier comparison between cohorts.

There is no doubt that any of the definitions, and the accompanying caveats, help in increasing awareness of resistant hypertension as well as focusing on further investigations and treatments. The problems arise, as will be discussed in the next section, when these definitions are interpreted in epidemiological research into the prevalence and impact of this condition, as well as interventional research.

Prevalence of Resistant Hypertension

The reported prevalence of resistant hypertension from population studies with blood pressure control data [31, 32], subpopulations of trials [33–39], retrospective analyses of registry data [15, 40, 41], and population studies specifically identifying patients with resistant hypertension [16, 42, 43] varies widely with estimates ranging from 3% to 34.3%. Pooled prevalence data from North American and European studies, with a combined sample size greater than 600,000 hypertensive patients, suggests the prevalence of resistant hypertension to be 14.8% of treated hypertensive patients [44]. Analysis of randomized controlled trials tends to give higher prevalence estimates than observational studies [29, 45]. This is likely to reflect selection bias with patients at higher cardiovascular risk being included and potentially lacks generalizability to the general hypertensive population. However, at least participation in a clinical trial provides robust data on prescribed doses not normally available from population studies.

In general, most definitions of resistant hypertension do not attempt to distinguish between resistant and pseudo-resistant hypertension: mainly patients with white coat syndrome, improper blood pressure measurements, and nonadherence to prescribed medication [44]. Indeed, one of the main challenges in establishing the prevalence of true resistant hypertension is excluding those patients with

pseudo-resistant hypertension [44]. When hypertension is defined as "a properly measured blood pressure > 140/90 mmHg with a mean 24-h ambulatory BP greater than 130/80 mmHg in a patient confirmed to be taking three or more antihypertensive medications," then the prevalence of "true" resistant hypertension is estimated to be lower at 10% of patients with treated hypertension [44].

In order to determine the true prevalence of resistant hypertension would require a prospective cohort study in a large hypertensive population with blood pressure control established by forced titration up to full doses of three different classes of antihypertensive agents, including a diuretic [44, 46]. Such a study would also need to establish adequate medication adherence, appropriate blood pressure measurements, and 24-h ambulatory blood pressure monitoring [44]. Such a study has been performed in a small ($n = 606$) group of young hypertensive patients in Brazil [47]. The initial prevalence of resistant hypertension defined as a blood pressure greater or equal to 140/90 mmHg despite treatment with three antihypertensive agents including a diuretic was 17.5%. However, this figure fell to 4.5% once adherence to medication had been established and 24-h ambulatory blood pressure measurements performed [47].

The American Heart Association definition [27] of resistant hypertension has been the one used by most studies. As discussed, in this definition patients with controlled blood pressure on four or more agents are considered to be the same as those with uncontrolled blood pressure on three or more agents. However, emerging evidence suggests that patients with controlled blood pressure have a "healthier" phenotype with less prevalence of diabetes mellitus and lower LDL-cholesterol than those with controlled blood pressure [28]. These kinds of potential differences need to be taken into account when interpreting the results of studies on patients with resistant hypertension, especially when considering which part of the definition defined the proportions of patients enrolled.

A significant amount of the variability in the prevalence of resistant hypertension may well also arise from inconsistent variations in the interpretation of the American Heart Association 2008 definition. This definition was devised to identify a subset of patients who might benefit from further investigations or treatments and not for research purposes [27]. A study interpreting the American Heart Association definition with different levels of "leniency" on a well-characterized hypertensive population found very different prevalence of resistant hypertension depending on the interpretation used (Fig. 1.1) [48]. After exclusion of patients with documented problems with adherence to medication, the prevalence of resistant hypertension decreased in a stepwise fashion from 30.9% to 3.4% with decreasing "leniency" of the definition interpretation. Interestingly, these figures approximate very closely with the highest (34.3%) and lowest (3.0%) reported prevalence of resistant hypertension, suggesting that differing interpretations of the definition may well explain a significant proportion of the variability.

Further evidence for this comes from another study in which half the patients with resistant hypertension were not receiving "optimal" therapy [42]. The definition of "optimal" in this study was not particularly severe, with patients only having to be on a diuretic and two other antihypertensive agents prescribed at doses greater

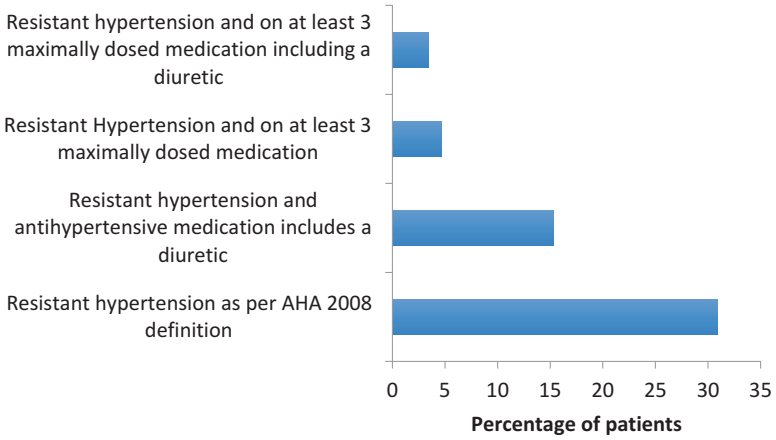

Fig. 1.1 Prevalence of resistant hypertension in a cohort of patients varies depending on the stringency of the definition used (Data from Hayek et al. [48]. The prevalence decreases when the American Heart Association (AHA) 2008 definition is applied at different levels of stringency)

or equal to 50% of the maximum recommended or approved doses for the treatment of hypertension. Indeed, in addition to the prescribing of inadequate doses of antihypertensive agents, other physician-associated factors, including poor office blood pressure measurement technique, inappropriate choice of antihypertensive combinations, clinical inertia, poor communication, and a lack of desire to invest in patient education, are all factors that have been associated with pseudo-resistant hypertension [29].

One of the aims of defining resistant hypertension has been to identify patients for further treatment. Few novel treatments for hypertension have attracted more interest, or indeed controversy, than renal denervation [49–51]. However, caution has to be applied when applying the results of these, and potentially other future studies, as the definitions for eligibility used are often much more stringent than the usual definitions of resistant hypertension [52–54]. Indeed, when the entry criteria to the SYMPLICITY-HTN-3 study [54] were applied to a hypertensive cohort with a reported resistant hypertension prevalence of 30.9%, only 0.8% would have been eligible for the trial [48].

Patient Characteristics Associated with Resistant Hypertension

It has long been recognized that blood pressure is more difficult to control in patients who are older, are diabetic, and have higher baseline blood pressure or longer duration of hypertension, history of cardiovascular disease, black race, obesity, and

Table 1.2 Patient factors associated with resistant hypertension

Older age, especially over 75
Higher baseline blood pressure
Chronicity of uncontrolled hypertension
Presence of target organ damage (left ventricular hypertrophy, albuminuria)
Black race
Diabetes mellitus
Obesity
Atherosclerotic vascular disease
Arteriosclerotic vascular disease
High dietary sodium
Chronic kidney disease

evidence of target organ damage including left ventricular hypertrophy and albuminuria [35]. It is, therefore, perhaps not surprising that all of these factors are consistently overrepresented in patients with resistant hypertension (Table 1.2) [15, 16, 19, 28, 43, 55, 56]. Consistent, and closely linked, with these findings, patients with resistant hypertension have a further clustering of other cardiovascular risk factors including reduced glomerular filtration rate, obstructive sleep apnea, physical inactivity, excess dietary salt, hyperlipidemia, and arteriosclerotic vascular disease [29, 30, 46].

Outcomes in Patients with Resistant Hypertension

The risk of stroke, myocardial infarction, chronic kidney disease, and heart failure rises proportionally with increasing blood pressure, whether treated or not [5, 13]. As discussed above, patients diagnosed with resistant hypertension consistently have an excess of cardiovascular risk factors as well as higher documented cardiovascular events. It is perhaps therefore not surprising that in observational studies, patients with resistant hypertension consistently have worse cardiovascular outcomes and increased mortality compared with other hypertensive patients [29, 30]. A large observational study showed that patients with resistant hypertension are 50% more likely to have an adverse cardiovascular outcome than other hypertensive patients [30]. Intriguingly, this increased risk appeared to be largely explained by the development of chronic kidney disease. What is perhaps less clear is whether having resistant hypertension in itself leads to an increase in cardiovascular risk factors, and consequent higher mortality, or whether an increased prevalence of cardiovascular risk factors leads to a higher prevalence of resistant hypertension. Conceivably these relationships are likely to be very complex and probably bidirectional.

Conclusions

Interest in resistant hypertension has been growing over the last few years with the increasing recognition of its prevalence and associated adverse outcomes. The definitions of resistant hypertension used up until now were derived mainly in response to the clinical need to identify these patients for further investigation, evaluation, and treatment. However, the patients so identified are likely to represent a large, amorphous group. As our understanding of this condition increases, it is likely that subgroups of patients with different characteristics and etiologies are identified. These will require different definitions and probably alternative investigational pathways and treatment strategies. To achieve this, there clearly is a need for further research into resistant hypertension. However, currently used definitions leave some subjectivity in the classification of patients with resistant hypertension. As a consequence, researchers will need to either more clearly define the condition, a move that might make it difficult to use in day-to-day clinical practice, or develop methodologies that create comparable baseline populations. These will need to, at the very least, include pathways or algorithms designed to identify patients with pseudo-resistance and secondary causes of hypertension to standardize the research population.

The adverse impact of resistant hypertension on patients and health economies is likely to increase with time. Its association with factors such as obesity, diabetes mellitus, and advancing age means that even if the prevalence of hypertension remains unchanged, the prevalence of resistant hypertension will continue to increase further. This is likely to occur in parallel, or even synergistically, with the predicted increases in chronic kidney disease worldwide.

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