

Resistant Hypertension in Chronic Kidney Disease

Adrian Covic
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*To my family for their unconditional support
and to my students for their permanent
challenge*

Adrian Covic

*To all my mentors and friends who
encouraged me to become a doctor and
eventually decide to pursue nephrology as a
career.*

*To my parents, my two lovely children, Sude
and Murat, and my very loving and
understanding wife, Asiye, who supported
and encouraged me in all steps of my life.*

Mehmet Kanbay

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Edgar V. Lerma

Foreword

Cardiovascular abnormalities are the major cause accounting for the increased morbidity and mortality in patients with chronic kidney disease. A wide range of factors participate to pathophysiologic mechanisms of cardiovascular complications including diabetes mellitus, vascular nephropathy, general aging of patients, and hypertension. Chronic kidney disease is frequently associated with resistant hypertension defined as blood pressure above optimal goal despite adherence to at least three optimally dosed antihypertensive medications (ideally RAS blocker, CCB), one of which is a diuretic. Recent advances led to increased understanding of causes, pathophysiology, diagnosis, and treatments of resistant hypertension in general populations. The epidemiology, prevalence, clinical characteristics, and outcomes associated with resistant hypertension in chronic kidney disease are less documented, and the aim of this book is to provide comprehensive and detailed review concerning the general workup in CKD-associated resistant hypertension.

The book comprises 22 chapters organized into four parts. The first part comprises six chapters dealing with definitions, epidemiology, characteristics, risk stratification, and outcomes of resistant and apparent treatment-resistant hypertension. The importance of ambulatory and home monitoring of blood pressure for diagnosis and evaluation of hypertension is emphasized in Chap. 4. In the second part, eight chapters cover the pathophysiology and the diagnosis of resistant hypertension, emphasizing the role of ambulatory blood pressure measurement to exclude white coat effect and checking for barriers to antihypertensive treatment (nonadherence or insufficient treatment, salt intake, interfering pressor substances or medications). Four chapters of the second part cover the screening for secondary causes of resistant hypertension, including the role of aging and sleep apnea syndrome. The third part comprises five chapters covering treatment of resistant hypertension in the light of new guidelines, including procedures and devices for neural modulation including renal denervation and barostimulation. The last part of three chapters covers public health approaches to resistant hypertension, excellent teaching program, and resistant hypertension for general practitioners.

This book brings up-to-date informations and is intended to assist nephrologists, internists, cardiologists, and general practitioners taking care of chronic kidney disease patients.

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Gérard Michel London

Preface

This book features practical, referenced information on the care of patients with resistant hypertension and chronic kidney disease. It covers some of the clinical aspects of renal care while also presenting important underlying pathophysiological principles. *Resistant Hypertension in Chronic Kidney Disease* provides a practical guide to diagnosis, understanding, and treatment of all adult patients.

For medical students, it can serve as an excellent resource for reference and review of resistant hypertension. Residents in internal medicine (and other specialties) and most especially, nephrology fellows in training, will appreciate the discussions of diagnostic and therapeutic approaches. General internists, family practitioners, hospitalists, nurses and nurse practitioners, physician assistants, and other allied health-care providers who work with patients with kidney diseases will find this as a very useful reference on management challenges posed by this condition. Moreover, patients and their family members who seek information about the nature of specific diseases and their diagnosis and treatment may also find this book to be a valuable resource.

Striking just the right balance between comprehensiveness and convenience, *Resistant Hypertension in Chronic Kidney Disease* emphasizes the important features of clinical diagnosis and patient management while providing a comprehensive discussion of pathophysiology and relevant basic and clinical science.

This book has been designed to meet the clinician's need for an immediate reference in the clinic as well as to serve as an accessible text for a thorough review of the current published guidelines.

We wish to thank our contributing authors for devoting their precious time and offering their wealth of knowledge in the process of completing this important book. These authors have contributed countless hours of work in regularly reading and reviewing the literature in this specialty, and we have all benefited from their clinical wisdom and commitment.

We would like to thank Elise Paxson for her assistance in managing the flow of manuscripts and materials among the chapter authors, editors, and publisher. This book would not have been possible without the help of Brian Halm, Maria David, Anupradhaa Subramonian, P. Vijay Shanker, and of course, the unwavering support of Gregory Sutorius.

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Chapter 1

Definitions of Resistant Hypertension and Epidemiology of Resistant Hypertension

Charles J. Ferro

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 anti-hypertensive 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.