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CHRONIC KIDNEY DISEASE (CKD) AND HYPERTENSION ESSENTIALS

Updated Guidelines from AHA, ASH, WHO, ISH, ESH, & ESC

Treating Hypertension in Advanced/ End-Stage CKD

Diagnosis and Management of Resistant Hypertension

Evaluating Kidney Function

2011

Andrew S. Bomback, MD, MPH
George L. Bakris, MD, FASN, FAHA

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CHRONIC KIDNEY DISEASE (CKD) AND HYPERTENSION ESSENTIALS

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2011

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Production Credits
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Cover Image: © Aaliya Landholt/ShutterStock, Inc.
Printing and Binding: Cenveo
Cover Printing: Cenveo

Library of Congress Cataloging-in-Publication Data
Bomback, Andrew.
Chronic kidney disease and hypertension essentials 2011 / Andrew Bomback, George Bakris.
p. ; cm.
Includes bibliographical references and index.
ISBN-13: 978-0-7637-8136-1
ISBN-10: 0-7637-8136-3
1. Chronic renal failure. 2. Hypertension. I. Bakris, George L., 1952- II. Title.
[DNLM: 1. Chronic Disease. 2. Kidney Diseases—complications. 3. Hypertension—complications.
WJ 300 B695c 2011]
RC918.R4B66 2011
616.6'14—dc22

2010002606

6048
Printed in the United States of America
14 13 12 11 10 10 9 8 7 6 5 4 3 2 1

DEDICATION

To our families.

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Dr. Bomback has published over 40 articles and book chapters on the subjects of chronic kidney disease and cardiovascular disease, with a specific focus on hypertension, diabetes, obesity, and glomerular diseases. He received the 2008 Alpha Omega Alpha Editor's Prize for his writing on kidney disease. He currently serves on the steering and publications committees for the National Kidney Foundation's Kidney Early Evaluation Program (KEEP). He is also the author of a medical novel, *You're Too Wonderful to Die*.

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Dr. George L. Bakris received his medical degree from the Chicago Medical School and completed his residency in internal medicine at the Mayo Graduate School of Medicine, where he also did a research fellowship in physiology and biophysics. He then completed fellowships in nephrology and clinical pharmacology at the University of Chicago. From 1988 to 1991, he served as the director of renal research at the Ochsner Clinic and was a faculty member of Tulane University School of Medicine. He was also a professor and the vice chairman of preventive medicine and director of the Rush University Hypertension Center in Chicago, Illinois, from 1993 until 2006. Currently, he is a professor of medicine and director of the hypertensive diseases unit in the Section of Endocrinology, Diabetes, Metabolism, and Hypertension at the University of Chicago, Pritzker School of Medicine.

Dr. Bakris has published over 470 articles and book chapters in the areas of diabetic kidney disease, hypertension, and progression of nephropathy. He is the editor or coeditor of 8 books in the areas of kidney disease progression and diabetes. He has also served as the coprincipal investigator of an NIH clinical research training grant (K30) to train clinical researchers (1999–2004). He chaired the National Kidney Foundation Consensus report on blood pressure and impact on renal disease progression (2000) and served on many national guideline committees, including writing committees of the Joint National Committee Writing Groups 6 and 7 (1997, 2003) and the JNC 7 executive committee (2003), the American Diabetes Association Clinical

Practice Guideline Committee (2002–2004), the National Kidney Foundation (K-DOQI) Blood Pressure Guideline committee (2002–2004), the National Kidney Foundation (K-DOQI) Diabetes Guideline committee (2003–2005), and the NIH National High Blood Pressure Education Program Working Group on Hypertension and Renal Disease (1994). He also served as an expert consultant to the Cardiorenal Advisory Board of the FDA (1993–2003). Dr. Bakris is also a past president of the American College of Clinical Pharmacology (2000–2002) and the president-elect of the American Society of Hypertension (ASH). He is the current editor of the *American Journal of Nephrology*, the hypertension section editor of *Up-to-Date*, and coeditor of the *Journal of Human Hypertension*.

FOREWORD

As a 68-year-old male former professor of medicine who exercises vigorously daily and is not overweight, I was disgruntled to learn from my physician that I have hypertension and must now swallow pills for the rest of my life. With that sentence, I join about half the persons (both genders) of my age. Many in the other half have hypertension but do not know it or have physicians less wise than mine. My physician argues that I may not have to die of heart failure the way my father did. At least I do not have kidney disease.

Of course, I read what is published in my field, and, as an educator, I am particularly interested in books about hypertension. This small volume focuses on hypertension and kidney disease. Kidney disease has been around since Richard Bright put it on the map (1820) and since Franz Volhard mapped the various kidney diseases (1914). Nonetheless, the role of the kidney in cardiovascular diseases and, in particular, as a risk factor coupled with hypertension received a much deserved emphasis when kidney disease was placed in front of the horizon of the other medical and ancillary professions. The same happened with heart disease, when the New York Heart Association put that condition on the map (circa 1939) by developing a functional scale that every doctor, even nephrologists and orthopedic surgeons, could understand (classes I–IV). The scale rests on very simple clinical grounds and does not require knowledge of Fick's principle. Van Slyke introduced the clearance method; however, unfortunately the relationship between filtration rate markers such as creatinine and filtration is hyperbolic. Few doctors can think in a hyperbolic fashion. The introduction of chronic kidney disease staging (which now is a job of the laboratory printout) classifies the patients in terms of stages 1–5. Those in stage 5 are treated with dialysis or should be. This amazingly simple method enables every physician to couple the risks of hypertension (and other risk factors) to the stage of chronic kidney disease and thereby greatly expands the power of risk assessment, a tool that was unheard of as little as 10 years ago. Chapter 1 explores the utility of this tool. We have known since antiquity that old people die faster than young ones. This revelation is now much more apparent because life expectancy has increased dramatically, dying in childbirth has become uncommon, and access to foodstuffs (aside from limitations related to military/political conflagrations) has increased. Race has a definite effect on hypertension and on renal disease risk, as Chapter 2 points out. Gender also affects kidney disease risk. Considering these differences goes far beyond political correctness, because research in the area is focusing on novel genetic causes that we may be able to someday address directly. Even age falls under this rubric. The Nobel Prize in medicine went to researchers who unraveled the telomeres and yes, there are many genes responsible for their function and maintenance.

Stephen Hales was the religious leader (pastor) who first measured blood pressure. He was rather direct about it, and his subject, a horse, apparently died from the attempt. In those days, everyone had to go to church, so pastors had leisure time for the other six days. The same, incidentally, was true for synagogues and mosques, so no wonder preachers got things done! Frederick Akhbar Mahomed was the first to apply a useful human blood pressure measurement. He commented: "Previous to the commencement of any kidney change, or to the appearance of albumin in the urine, the first condition observable is high tension in the arterial system." Herein lies the essence of Chapter 3! Samuel von Basch, Scipione Riva-Rocci, Nikolai Korotkoff,

and Harvey Cushing brought the technical measurement of blood pressure to the patients, who now include me. One hundred years later, we still argue and are uncertain about how exactly albuminuria occurs. However, we are united in our belief that it is bad! In the latter 19th century, Henri Huchard concluded: "It has been wrongly assumed that chronic hypertension only appears following interstitial nephritis. The opposite is true; arterial hypertension is the cause of arteriosclerosis; it precedes by a varying time interval the evolution of different diseases, heart disease and arterial nephritis."

Where would we be without Harry Goldblatt? He is largely responsible for Chapter 4. This meticulous pathologist was just a better scientist than his competitors, and he did it right. He proved that renin release, as Robert Tigerstedt had proposed, causes hypertension and showed how this phenomenon came about. His model led to clarifying renin, elucidating angiotensinogen, identifying angiotensin (Ang) II, and all the things that came later. Also in the cards was the identification of a relationship between Ang II and the salt-retaining hormone aldosterone, first suggested by Franz Gross. The next chapter deals with the fallout from that research. Franz Volhard, who believed that benign hypertension was "red," while malignant hypertension was "white," clinically elucidated resistant hypertension and its sequelae. Any political resemblance to the Russian revolution (1917 and onwards) is coincidental. The chapter leads us directly to the irritating question of: "What exactly is secondary hypertension?" With the wave of obesity (secondary) and related complications coming upon us, is this Tsunami tidal wave secondary?

Increasingly large numbers of persons worldwide are faced with renal replacement therapies because they have reached chronic kidney disease stage 5. This sad state of affairs is not a death sentence. However, it is almost a death sentence! Dialysis patients have a mean survival (I am talking about rich countries) of less than 5 years. With kidney transplantation, this survival is increased, but not by much. The entire organ transplantation imbroglio is involved in its own controversies. What can be done here? We do not know. The deaths of dialysis patients are cardiovascular, but not of the sort that give our cardiologist friends much pleasure or profit. Dialysis patients do not usually present to the doctor with "acute coronary syndromes." Statins do not appear to help them. The utility of percutaneous coronary interventions is uncertain. The steady increase of diabetic dialysis patients adds more confounding variables and confusions. Blood pressure goals—indeed, how or when to measure blood pressure in these patients—add to the mystery. What tablets to swallow, if any, confounds the conclusions. At the risk of taking a beating from my friends in the "evidence-based medicine" crowd, I would like to relate a personal anecdote. The physician who runs my (erstwhile) dialysis unit is a dialysis patient himself. He performs dialysis on himself nightly (and has done so for more than 20 years). His blood pressure is normal. He is not quite as old as I am (so he still has a job), but almost. He has to eat high-phosphate foods, but I advised him not to drink "Coke."

I like lifestyle changes, particularly my own, so here we are in Chapter 6. Franz Volhard wrote more about hypertension (even more than George Bakris), but he could do very little about it. I recently checked out his recommendations from 1940. He gave the patients with malignant hypertension "strophanthin" (intravenous form of acute digitalis), put them to bed, and put them on "food rest." He fed them nothing! It worked. When the patients claimed that they would rather die than live on nothing, he next gave them a "salt free" diet. Walter Kempner applied this idea 20 or so years later and thereby put Duke University on the map (I apologize to Victor Dzau). The diet people have come and gone in legions since then. I grew up in the Texas hill country and in Albuquerque, New Mexico. I attended public schools. From first

grade, we had physical education in every grade (1 hour per day). We played competitive sports. Our "coach," who also taught several other classes, would not allow pupils "whom he caught smoking" to participate on any competitive teams. Our school lunch program was a "brown bag" prepared by mom. To drink, there was the "drinking fountain." Moreover, we did not know what a "pop" machine was. I was the "fatso" in the class. I believe that I grew up in a "lifestyle" environment that has unhappily disappeared from the scene (in all countries). In addition, I learned the words to "The Eyes of Texas are Upon You." Approaching persons my age (or three decades younger) to instruct them on their behavior is illusionary. A brief look at the Diabetes Prevention Program, interpreted as a great victory by the authors, makes my point. Is there any political willingness to attack this problem? Next is the problem of what tablets to swallow. For me personally, this is not a problem. I open the package from the pharmacy when I get home and eat the stuff the way my doctor prescribed it. I hope that my doctor is not spending his vacation on Mallorca (or your favorite vacation spot) on my account! I say, "Just eat the damn stuff!"

I have a secret for you: "There are no controversies!" Controversies have to do with global warming, top quarks, space and time (I believe Einstein fixed that one), and whether or not to purchase an iPhone. We can beat our heads against the wall about 5–10 mm Hg for this and that. We can argue about the (pro)renin receptor and whether or not hydrochlorothiazide is as good as chlorthalidone, about which all thiazide conclusions are based. Alternatively, we can quiver about beta-blockers, because the favorite whipping boy (or girl) for all major drug comparison studies was atenolol. I am now a consumer. I want to know if my blood pressure is okay (I have an oscillometric device to measure it). I am interested in my other risk factors, namely what opponents have annoyed me lately, and my wife is concerned that I drink too much (she is not talking about water) and what my cholesterol concentration might be.

To whom would I recommend this book? First, all former professors of medicine should read this book, provided that they are still reading. The book is a very worthwhile compendium for physicians in training (medical students, house staff, and fellows) and those of us who take CME seriously (those murderous examinations by ABIM—yes you can check me out). I enjoyed this sojourn through hypertension.

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Chapter 1

Definitions of Hypertension in Chronic Kidney Disease

Chronic kidney disease (CKD), defined by the National Kidney Foundation as the presence of kidney damage or decreased level of kidney function for at least 3 months, is a worldwide public health problem with a rising incidence and prevalence. Currently, over 26 million American adults (approximately 17% of the adult population) have CKD,[1,2] which is staged according to glomerular filtration rate (GFR) and the presence or absence of kidney damage, defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies (**Table 1.1**).[3] There is growing evidence that some of the adverse outcomes of CKD—in particular, progression to overt renal failure and development of cardiovascular disease—can be prevented or delayed by early detection and appropriate treatment. Effective diagnosis and management of hypertension is a crucial component of such efforts.

Hypertension is both a common cause and complication of CKD. In the United States, hypertension is the second leading cause of CKD (second only to diabetes) and is present in up to 80% of individuals with moderate to severe kidney disease (**Figure 1.1**). The appropriate evaluation and treatment of hypertension is critical in caring for patients with CKD, as uncontrolled blood pressure can lead to faster decline in kidney function and accelerated development of cardiovascular disease, the leading cause of death for CKD patients.

Blood pressure should be viewed as a continuous variable with a continuous rise in cardiovascular risk beginning at systolic blood pressure levels $>$ 115 mm Hg.[4] The clinical diagnosis of hypertension, therefore, is arbitrary to a certain extent. By convention, this diagnosis has been assigned to patients with blood pressure levels maintained above 140 mm Hg systolic and/or 90 mm Hg diastolic, but appropriate management of hypertension involves recognition that the risks of high blood pressure do not suddenly begin above these and other numbers put forth in guidelines.

GUIDELINES

The *Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)*, published in 2003,[5] classifies blood pressure for adults based on the average of 2 or more properly measured, seated blood pressure readings

Table 1.1. The five stages of chronic kidney disease

Stage	Description	GFR (ml/min/1.73 m^2)
1	Kidney damage[a] with normal or ↑ GFR	$\geq$ 90
2	Kidney damage[a] with mild ↓ GFR	60–89
3	Moderate ↓ GFR	30–59
4	Severe ↓ GFR	15–29
5	Kidney failure	$<$ 15 (or dialysis)

[a] Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies (e.g., albuminuria).

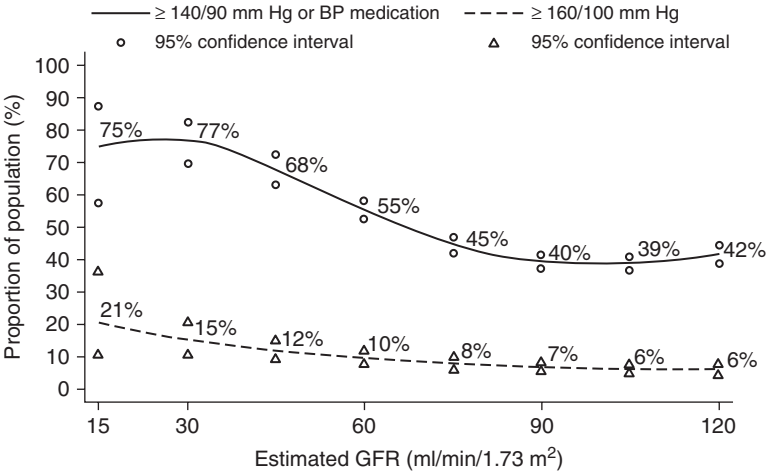

Figure 1.1. Predicted prevalence of hypertension among adult participants (> 20 years) in the Third National Health and Nutrition Examination Survey (NHANES III) by level of GFR. Values are adjusted to age 60 years using a polynomial regression.

Source: K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Am J Kidney Dis.* 2002;39(2 suppl 1):S1-266. Reprinted with permission from the National Kidney Foundation.

on each of 2 or more office visits (**Table 1.2**). The *JNC 7* categorizes blood pressure as normal (systolic blood pressure [SBP] < 120 mm Hg and diastolic blood pressure [DBP] < 80 mm Hg), prehypertension (SBP 120–139 mm Hg or DBP 80-89 mm Hg), stage 1 hypertension (SBP 140–159 mm Hg or DBP 90–99 mm Hg), and stage 2 hypertension (SBP ≥ 160 mm Hg or DBP ≥ 100 mm Hg). This report includes a new category of prehypertension to identify patients who are at increased risk for progression to hypertension and who require health-promoting lifestyle modifications to prevent cardiovascular disease.

The *JNC 7* includes a separate recommendation for patients with CKD, defined by either reduced GFR or presence of albuminuria (> 300 mg/day on 24-hour urine collection or > 200 mg albumin/g creatinine on spot morning urine collection). For these patients, the goal blood pressure target is < 130/80 mm Hg, lower than the recommended blood pressure in uncomplicated hypertension. Aggressive blood pressure management, often with 3 or more drugs, is encouraged to achieve this lower blood pressure target. The same blood pressure goal of < 130/80 mm Hg is recommended for patients with diabetes, with or without concomitant kidney disease. The *Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* (*JNC 8*) is projected to

Table 1.2. Classification of blood pressure for adults according to JNC 7

Blood pressure classification	Systolic BP (mm Hg)	Diastolic BP (mm Hg)
Normal	< 120	and < 80
Prehypertension	120–139	or 80–89
Stage 1 hypertension	140–159	or 90–99
Stage 2 hypertension	≥ 160	or ≥ 100

be released in the fall of 2010. While the prospective data defining this goal pressure is not supportive unless the patient has an estimated GFR (eGFR) below 45 ml/min/1.73 m^2 and more than 300 mg/day of albuminuria, the goal blood pressure for CKD patients is not expected to change.

Other guidelines have also stressed different definitions and treatment goals for hypertension in patients with CKD. The American Heart Association targets a blood pressure $<$ 130/80 mm Hg for patients with high coronary artery disease risk, which includes patients with CKD.[6] Guidelines from the World Health Organization (WHO) and International Society of Hypertension suggest the same goal blood pressure of $<$ 130/80 mm Hg for patients with renal insufficiency, diabetes, and established heart disease.[7] The British Hypertension Society, in collaboration with the National Institute for Health and Clinical Excellence, issued a clinical guideline on the management of hypertension (available at www.nice.org.uk/CG034) that reviews the available evidence on lower blood pressure targets for patients with CKD without making overt recommendations. Likewise, the second set of guidelines produced jointly by the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) do not explicitly recommend a lower target blood pressure for patients with CKD, noting that "evidence from trials having randomized renal patients to more versus less intensive blood pressure lowering is scanty."[8] Nonetheless, these guidelines still highlight the very high added risk for cardiovascular disease in such patients (equivalent to the risk in patients with preexistent cardiovascular disease) at all levels of blood pressure (**Figure 1.2**).

This last statement marks perhaps the most important message of these various guidelines and this book. Patients with CKD are at heightened risk for premature morbidity and mortality from cardiovascular disease; indeed, these patients are far more likely to die from heart disease than progress to end stage renal disease. The management of hypertension in CKD patients is crucial for reducing this excessive cardiovascular disease burden. Later, we will explore the evidence on lower goal blood pressures in CKD; as the ESH-ESC guidelines note, much of the evidence is based on observational and post hoc analyses. What is less controversial, however, is the *JNC 7* recommendation for aggressive blood pressure therapeutic regimens that often incorporate multiple agents, as this heightened effort toward lowering blood pressure, regardless of a targeted number, is perhaps the most salient intervention in the care of CKD patients.

Blood pressure (mm Hg)					
Other risk factors, OD, or disease	Normal SBP 120-129 or DBP 80-84	High normal SBP 130-139 or DBP 85-89	Grade 1 HT SBP 140-159 or DBP 90-99	Grade 2 HT SBP 160-179 or DBP 100-109	Grade 3 HT SBP ≥ 180 or DBP ≥ 110
No other risk factors	Average risk	Average risk	Low added risk	Moderate added risk	High added risk
1-2 risk factors	Low added risk	Low added risk	Moderate added risk	Moderate added risk	Very high added risk
3 or more risk factors, MS, OD, or diabetes	Moderate added risk	High added risk	High added risk	High added risk	Very high added risk
Established CV or renal disease	Very high added risk	Very high added risk	Very high added risk	Very high added risk	Very high added risk

Figure 1.2. The stratification of cardiovascular risk into four categories in the ESH-ESC guidelines. Low, moderate, high and very high risk refer to 10-year risk of a cardiovascular fatal or nonfatal event. The term "added" indicates that in all categories risk is greater than average. The dashed line indicates how the definition of hypertension may be variable, depending on the level of total cardiovascular risk. SBP: systolic blood pressure; DBP: diastolic blood pressure; cv: cardiovascular; HT: hypertension; OD: sub-clinical organ damage; MS: metabolic syndrome.

Source: Reprinted with permission from Mancia G, De Backer G, Dominiczak A, et al. 2007 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.* 2007;28(12):1462–1536 with permission from Oxford University Press.

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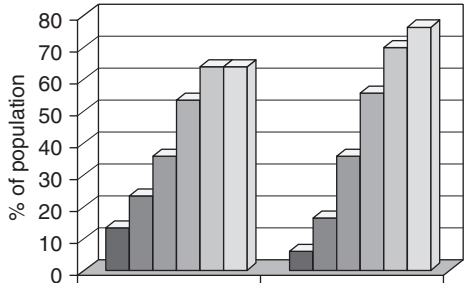
Chapter 2

Epidemiology of Hypertension in Chronic Kidney Disease

Prevalence rates of hypertension in the US adult population have risen remarkably over the past 2 decades but appear to have plateaued, according to data from the National Health and Nutrition Examination Survey (NHANES). The prevalence rates of hypertension among US adults were 27% in 1999–2000, 26% in 2001–2002, 29% in 2003–2004, and 29% in 2005–2006.[1,2] An additional 25–37% of US adults had prehypertension during this time period. There is significant variation in the prevalence of disease with age, gender, and ethnicity. In addition, as mentioned in the previous chapter, the prevalence of hypertension rises among patients with reduced renal function; up to 75% of patients with moderate to severe kidney disease have hypertension.

AGE

While the most recent NHANES data shows that roughly 1 in 3 American adults has high blood pressure, there is a clear, stepwise increase in hypertension prevalence with advancing age (**Figure 2.1**). The rising prevalence of hypertension with advancing age appears more



	Men	Women
20-34	13.4	6.2
35-44	23.2	16.5
45-54	36.2	35.9
55-64	53.7	55.8
65-74	64.7	69.6
75+	64.1	76.4

Figure 2.1. Prevalence of hypertension—defined as systolic BP > 140 or DBP > 90 mm Hg, use of antihypertensive medication, or physician diagnosis of hypertension—in adults by age and sex (NHANES 2005–2006 Data).

Source: Adapted from Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* 2009;119(3):e21–181.

prominent in females than in males, to the extent that diagnosed hypertension is more common among older women than among older men. Whereas hypertension rates among men aged 20–44 ranges from 13% to 23% compared to rates of 6–17% among comparably aged women, the prevalence of hypertension among women 65 and older is over 70% compared to an approximately 65% prevalence rate among men 65 and older.[2]

Not only the prevalence, but also the pattern of blood pressure elevation changes with age. Before reaching 50 years of age, most people with hypertension have elevated diastolic pressure. After age 50, as systolic pressure continues to rise and diastolic pressure tends to fall (**Figure 2.2**), isolated systolic hypertension predominates. The phenomenon is explained by an age-related decline in elasticity and compliance of large arteries from atherosclerosis-associated accumulation of arterial calcium and collagen and the degradation of arterial elastin.[3] Elevated systolic blood pressure is a stronger risk factor for both cardiovascular and kidney

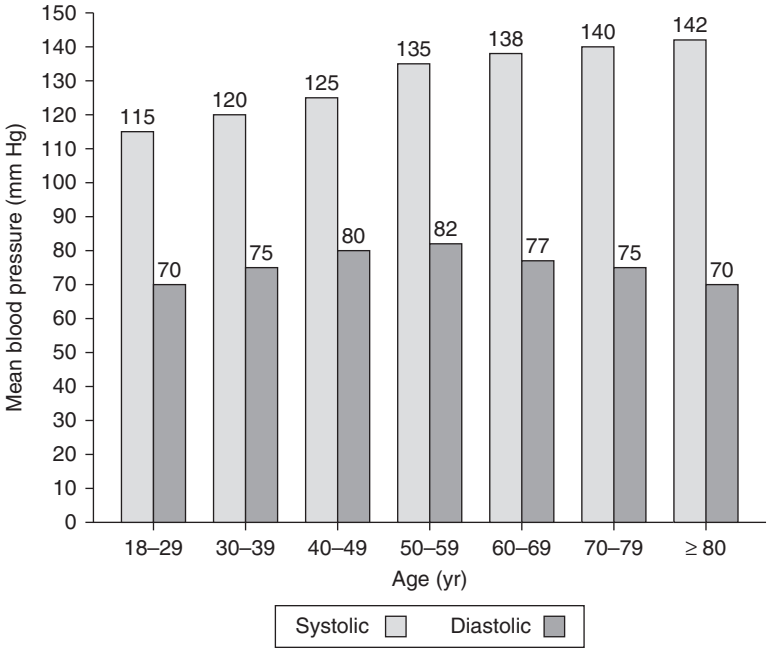


Figure 2.2. Mean blood pressure according to age in US adults (data from NHANES 1988–1991).

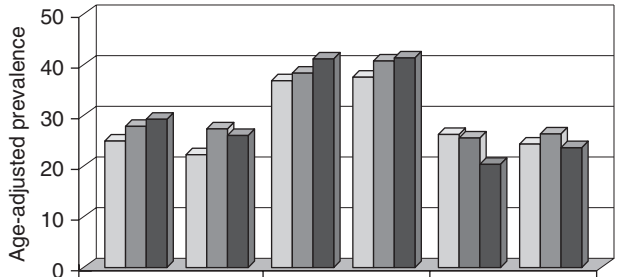
Source: Adapted from Chobanian AV. Clinical practice. Isolated systolic hypertension in the elderly. *N Engl J Med.* 2007;357(8):789–796.

disease than elevated diastolic pressure,[4] regardless of age; therefore treating elderly patients with hypertension, including isolated systolic hypertension, should still confer benefit.[5]

RACE/ETHNICITY

The prevalence of hypertension among African Americans is among the highest in the world and continues to rise. From 1994 to 2006, the prevalence of hypertension among African American men rose from 38% to 42%; by comparison, during this same time period, the hypertension rates among non-Hispanic white men rose from 26% to 30%, and rates among Mexican American men fell from 27% to 21%. Similar trends are apparent for African American women, among whom hypertension rates rose from 38% in 1988–1994 to 42% in 2005–2006. During this period, the prevalence of hypertension among white women rose from 23% to 27% and among Mexican American women fell from 25% to 24% (**Figure 2.3**).[2]

Compared with whites, African Americans develop high blood pressure earlier in life, and hypertension is typically more severe with regards to target organ damage in African Americans



	White		African American		Mexican American	
	Men	Women	Men	Women	Men	Women
1988–1994	25.6	22.9	37.5	38.2	26.9	25
1999–2004	28.5	28	39	41.4	26.2	27
2005–2006	29.9	26.7	41.8	42	21	24.3

Figure 2.3. Age-adjusted prevalence trends for hypertension in US adults by race/ethnicity (white, African American, Mexican American), sex, and NHANES survey years.

Source: Adapted from Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* 2009;119(3):e21–181.

than in whites.[6] Data from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study suggests that public health efforts to increase awareness of hypertension among African Americans have been successful (31% greater odds for awareness of prevalent hypertension in African Americans relative to whites), as have efforts to communicate the importance of receiving antihypertensive therapy (69% greater odds in African Americans versus whites).[7] However, despite slightly higher levels of awareness and treatment of hypertension, African Americans nonetheless have higher average blood pressures than whites, are less likely to have their blood pressures controlled (i.e., under 140/90 mm Hg with therapy), and suffer significantly greater rates of hypertensive-associated complications including stroke (fatal and nonfatal), heart disease death, and end stage kidney disease.

A recent study from the Multi-Ethnic Study of Atherosclerosis examined the differences in blood pressure within ethnic groups. In this population-based cohort of almost 7,000 men and women aged 45–84 years, of whom approximately 38% are white, 28% African American, 23% Hispanic, and 11% Asian (of Chinese descent), being born outside the United States, speaking a language other than English at home, and living fewer than 10 years in the United States were associated with a decreased risk for hypertension.[8] These results suggest that acculturation and place of birth are associated with hypertension, seemingly implicating the so-called Western lifestyle in the pathogenesis of hypertension for certain ethnic and racial groups.

MORBIDITY AND MORTALITY

Untreated and undertreated hypertension is associated with significant cardiovascular morbidity and mortality. Hypertension is an independent risk factor for the development of all of the clinical manifestations of cardiovascular disease, including coronary artery disease, peripheral vascular disease, congestive heart failure, and stroke. Data from 3 large, epidemiologic cohorts (Atherosclerosis Risk in Communities Study, Cardiovascular Health Study, and Framingham Heart Offspring Study) suggest that approximately 70–80% of people who have a first heart attack or stroke have blood pressure levels above 140/90 mm Hg, and about 3 in 4 patients with congestive heart failure have similar blood pressure elevations.[2] Hypertension was associated with shorter overall life expectancy in the Framingham Heart Study; compared with hypertensive individuals, total life expectancy was 5.1 and 4.9 years longer for normotensive men and women, respectively. Additionally, elevated blood pressure was associated with more years lived with cardiovascular disease.[9]

Hypertension predicts cardiovascular events in a continuous, graded manner. An oft-cited meta-analysis of 61 prospective studies with 1 million adult participants demonstrated that, starting from a level of 115/75 mm Hg, each 20/10 mm Hg increase in blood pressure essentially doubles overall cardiovascular risk.[10] By age 50, the overall lifetime risk of a cardiovascular event for a man with stage 1 or 2 hypertension approaches 65%, compared to a 48% risk for men with prehypertension and 47% risk for men with normal blood pressure at the same age. For women aged 50, the median life expectancy decreases from 37 years to 31 years as blood pressure increases from normal to hypertensive ranges, and lifetime cardiovascular risk increases from 29% to over 50% (**Table 2.1**).[11] The effect of hypertension on cardiovascular

Table 2.1. Lifetime risk for cardiovascular disease and median survival for men and women according to blood pressure at age 50

	Men			Women		
	Lifetime Risk for Cardiovascular Disease		Median Survival	Lifetime Risk for Cardiovascular Disease		Median Survival
Systolic or Diastolic BP, mm Hg	to 75 years (%)	to 95 years (%)	Years	to 75 years (%)	to 95 years (%)	Years
< 120 or < 80	26.6	47.3	33	10.5	29.3	37
120–139 or 80–89	31.8	47.9	32	17.9	37.0	36
140–159 or 90–99	46.4	61.6	29	28.8	52.3	35
≥ 160 or ≥ 100 or treated	51.3	65.1	28	35.0	50.6	31

Source: Data from the Framingham Heart Study; Table adapted from Lloyd-Jones DM, Leip EP, Larson MG, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation*. 2006;113(6):791–798.

events stretches to younger ages, too. In a prospective study of about 11,000 men aged 18 to 39 years in the Chicago area, followed for an average of 25 years, the relative risks for coronary heart disease were 2.07 (95% CI 1.13–3.77), 2.60 (95% CI 1.16–5.84), and 4.25 (95% CI 1.96–9.22) for subjects with baseline systolic blood pressures 160–169, 170–179, and ≥180 mm Hg, respectively.[12]

SYSTOLIC VERSUS DIASTOLIC BLOOD PRESSURE

For the majority of patients, the risk we attribute to hypertension is driven primarily by the systolic pressure. Systolic blood pressure is the major determinant of cardiovascular and renal events, particularly in patients over the age of 50.[13] For example, among 347,978 men screened for participation in the Multiple Risk Factor Intervention Trial, the risk of fatal stroke for those with systolic blood pressure over 180 mm Hg was about 15 times as high and the risk of fatal ischemic heart disease 7 times as high as the rates among those with optimal blood pressure.[14]

As mentioned previously, treating elderly patients with isolated systolic hypertension is beneficial, although treatment goals may need adjustment relative to low diastolic levels. The recent Hypertension in the Very Elderly Trial bore this out among nearly 4000 patients with mean age 83.6 years and mean baseline sitting blood pressure of 173.0/90.8 mm Hg. At 2 years, the mean blood pressure was 15.0/6.1 mm Hg lower in the active antihypertensive treatment group than in the placebo group, and active treatment was associated with a 30% reduction in the rate of fatal or nonfatal stroke, a 39% reduction in the rate of death from stroke, a 21% reduction in the rate of death from any cause, a 23% reduction in the rate of death from cardiovascular causes, and a 64% reduction in the rate of heart failure.[15]

Controversy exists as to the importance of pulse pressure—the difference between systolic and diastolic pressures—in predicting future events. Speculatively, while elevated systolic pressures cause left ventricular hypertrophy and increased oxygen demand, reduced diastolic pressures allow for less coronary perfusion time. Initial studies suggested that pulse pressure was a powerful predictor of cardiovascular risk.[16,17] A report from the Framingham Heart Study, for example, noted that a 16 mm Hg increment in pulse pressure conferred a 55% increased risk for congestive heart failure. However, more recent analyses suggest that the significance of the pulse pressure is lessened after adjusting for the systolic pressure.[18,19]

J-CURVE

Hypertension experts continue to debate the consequences of excessively lowering blood pressure in patients with hypertension. The seemingly paradoxical increase in morbidity and mortality as blood pressures fall below a certain threshold has been popularized as the J-curve (**Figure 2.4**).[20–24]

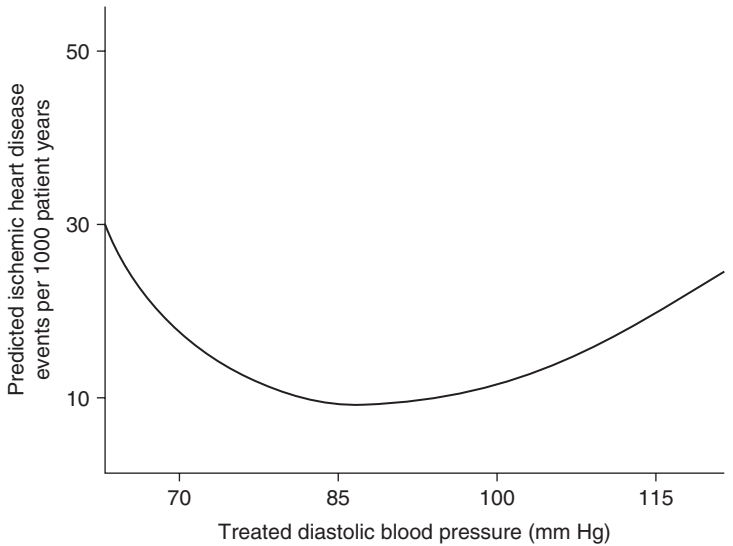


Figure 2.4. J-curve relationship between treated diastolic blood pressure and cardiovascular events, suggesting a J-point of 84–85 mm Hg.

Source: Adapted from Cruickshank JM. Antihypertensive treatment and the J-curve. *Cardiovasc Drugs Ther.* 2000;14(4): 373–379 with data based on seven anti-hypertensive treatment studies (n=1450) as analyzed in Farnett L, Mulrow CD, Linn WD, Lucey CR, Tuley MR. The J-curve phenomenon and the treatment of hypertension. Is there a point beyond which pressure reduction is dangerous? *JAMA.* 1991;265(4):489–495.

Cruickshank concluded that the J-point was about 85 mm Hg diastolic blood pressure but that the J-curve phenomenon was limited to hypertensive patients with preexistent heart disease.[25,26] A meta-analysis of data from more than 40,000 subjects argues that the increased risk for events observed in patients with low blood pressure was not related to antihypertensive treatment and not specific to blood pressure-related events.[20] Rather, overall poor health can lead to low blood pressure, and these comorbidities likely explain the increased risk for death, independent of blood pressure level and use of blood pressure–lowering therapy.

RISK FACTORS

The diagnosis of hypertension does not occur in isolation for most patients with high blood pressure. Indeed, hypertension is typically found alongside other well-known cardiac risk factors, including glucose intolerance, obesity, left ventricular hypertrophy, and dyslipidemia; and less than 15% of coronary events in hypertensive patients occur in the absence of additional risk factors.[27] Traditional cardiac risk factors for coronary disease include diabetes, hypertension, family history of early heart disease (before age 55 in men and before age 65 in women), tobacco use, and advanced age. Nontraditional risk factors—sometimes called "non-Framingham" risk factors in reference to the widely used Framingham risk score for cardiovascular disease[28]—that often accompany hypertension include obesity, the metabolic syndrome, and chronic kidney disease (CKD) (**Table 2.2**).

Over the last 3 decades, obesity prevalence has more than doubled among US adults. In the most recent NHANES data, 32.2% of US adults had a body mass index (BMI) $\geq$ 30 kg/m^2, which met the clinical criteria for obesity.[29] The rising prevalence of obesity has been matched by a parallel increase in the prevalence of metabolic syndrome. This clinical syndrome, marked by abdominal obesity (waist circumference $>$ 102 cm for men and $>$ 88 cm for women), hypertriglyceridemia ($\geq$ 150 mg/dl), low HDL cholesterol ($<$ 40 mg/dl in men or $<$ 50 mg/dl in women), elevated blood pressure ($\geq$ 130/85 mm Hg), and impaired insulin sensitivity (fasting glucose $\geq$ 110 mg/dl), is detectable in roughly 1 in 3 US adults.[30] Obesity, particularly

Table 2.2. Major cardiovascular risk factors according to the JNC 7

Hypertension
Cigarette smoking
Obesity (body mass index $\geq$ 30 kg/m^2)
Physical inactivity
Dyslipidemia
Diabetes mellitus
Microalbuminuria or estimated GFR $<$ 60 ml/min/1.73 m^2
Age ($>$ 55 years for men, $>$ 65 years for women)
Family history of premature cardiovascular disease (55 years for men, $<$ 65 years for women)

visceral obesity, leads to several physiologic changes, including endothelial dysfunction, overactivation of the sympathetic nervous system and the renin angiotensin aldosterone system, sodium retention, and increased oxidative stress.[31,32] This constellation of pathophysiologic mechanisms likely accounts for metabolic syndrome predicting a twofold to fourfold increase in the risk of cardiovascular disease and death,[33,34] an increased risk that in turn may vary by the presence and degree of hypertension.[35]

Chronic kidney disease is associated with accelerated cardiovascular disease risk, even when kidney function is only mildly impaired.[36,37] As noted earlier, patients with CKD are far more likely to die of cardiovascular disease than to progress to end stage renal disease. This increased risk is often attributed to a litany of traditional cardiovascular risk factors—hypertension, diabetes, tobacco abuse, advanced age—that frequently accompany reduced renal function. Several large studies have demonstrated that reduced kidney function is associated with higher blood pressure, higher total cholesterol, and lower HDL, and patients with CKD, compared to patients with preserved renal function, are more likely to have ischemic heart disease and overt heart failure.[38] Among patients with CKD, the presence of hypertension increases the risk of new or recurrent cardiovascular events by about twofold; of the traditional cardiac risk factors, only diabetes appears to confer more of an increased risk (about threefold).[39]

However, impaired kidney function itself is now considered an independent cardiovascular risk factor. In addition, CKD can be accompanied by a slew of nontraditional risk factors such as anemia, abnormal calcium-phosphorus metabolism, chronic inflammation, and hyperhomocysteinemia that can contribute to the excess cardiovascular risk associated with kidney dysfunction. Therefore, all patients with hypertension should be formally assessed for kidney disease. This assessment is the subject of the following chapter.

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Chapter 3

Assessment of the Hypertensive Patient for Kidney Disease

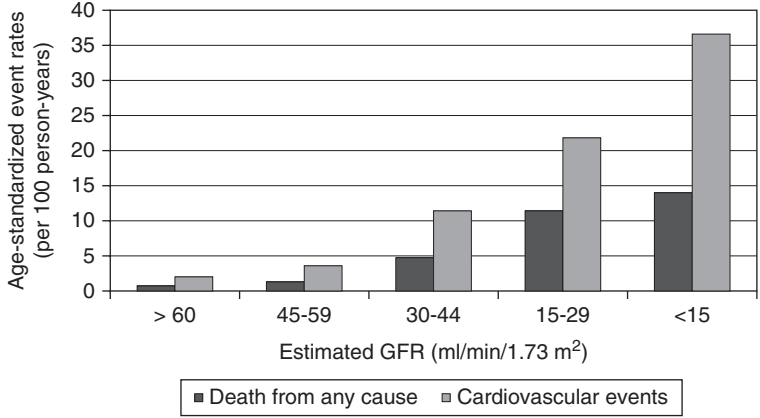

Figure 3.1. Age-standardized rates of death from any cause and cardiovascular events according to estimated GFR among 1,120,295 ambulatory adults in the Kaiser Permanente registry.

Source: Adapted from Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;351(13):1296–1305.

Classification of disease risk related to blood pressure is strongly affected by interactions with other risk factors, such as diabetes, advanced age, obesity, dyslipidemia, and smoking. The presence or absence of chronic kidney disease (CKD) is a key risk factor for clinicians to assess, as morbidity and mortality related to cardiovascular disease are higher for individuals at all CKD stages than for the general population. In an oft-cited study of over 1 million adults in the Kaiser Permanente registry, the risk of hospitalization, cardiovascular events, and death increased linearly as the estimated glomerular filtration rate (GFR) decreased below 60 ml/min/1.73m^2 (**Figure 3.1**).[1] Therefore, healthcare providers should evaluate their patients for the presence of CKD as part of preventive care and treatment strategies. This evaluation is particularly critical for patients with hypertension.

BLOOD PRESSURE MEASUREMENT

Accurate measurement of blood pressure is arguably the most important component of evaluating hypertension and its consequences, as even small differences in blood pressure are associated with modifiable disease risk. The American Heart Association recommends that multiple office blood pressure measurements be obtained and include at least 2 readings obtained at least 1 minute apart and within 5 mm Hg of each other.[2] The patient should be

seated comfortably, legs uncrossed and touching the floor, with the back supported and the upper arm exposed without clothing. The arm should be supported at heart level, and neither the patient nor the clinician should talk during the measurement.

There is increasing evidence that office blood pressure, as currently used in everyday practice, has major shortcomings. The limitations of office blood pressure measurement, detailed in a recent position paper from the American Society of Hypertension, include the inherent variability of blood pressure relative to the paucity of readings typically taken in a doctor's office and poor measurement technique (e.g., rapid cuff deflation, improper cuff size). In addition, the phenomena of "white coat" and "masked" hypertension, discussed later, cannot be assessed with office blood pressure measurements alone.[3] Consequently, out-of-office blood pressure monitoring to supplement office blood pressure measurements has become increasingly important.

Out-of-office monitoring can be done at home with self-blood pressure monitors, available for purchase at most drug stores, and with 24-hour ambulatory blood pressure monitoring. The use of self-monitoring, home blood pressure devices is growing rapidly, evidenced by a 2005 Gallup poll in which more than 50% of patients reported monitoring their blood pressures at home. Home blood pressure measurements allow detection of white coat hypertension, the increase of blood pressure that occurs in medical settings, and masked hypertension, the decrease of blood pressure that occurs in medical environments that covers out-of-office hypertension and often leads to undertreatment. In general, when there is a discrepancy between the office and home blood pressure, the risk for hypertensive complications follows the home blood pressure more closely. Consequently, patients with white coat hypertension are at relatively lower risk than their office blood pressures suggest, while patients with masked hypertension are at relatively higher risk.[4]

Ambulatory blood pressure monitors (ABPMs) take readings at preset intervals (e.g., every 30 minutes) throughout the day and night, providing a full profile of blood pressure and its variability over 24 hours (**Figure 3.2**).[5] A number of prospective studies have shown that 24-hour ABPM is the best method for estimating a patient's hypertension-related cardiovascular risk.[6–10] While some of the latest models of home blood pressure monitors can be programmed to take readings at preset times, which might include during sleep, the major distinction between ambulatory and home blood pressure monitoring remains the ability to capture nighttime blood pressures and the related measures of blood pressure dipping with ABPM (**Table 3.1**).

Nighttime pressure has been found to be an independent and, potentially, the most potent predictor of cardiovascular risk. In an Irish study of over 5000 untreated hypertensive patients, the relative hazard ratio for each 10 mm Hg increase in systolic blood pressure was 1.12 (1.06–1.18) for daytime and 1.21 (1.15–1.27) for nighttime pressure.[11] A larger cohort of 7458 patients from Europe, Asia, and South America found that nighttime blood pressure, adjusted for daytime pressure, predicted total, cardiovascular, and noncardiovascular mortality, yet daytime blood pressure, adjusted for nighttime pressure, only predicted noncardiovascular mortality.[12] In both normotensive and hypertensive individuals, blood pressure normally falls, or dips, during the night approximately 15% lower than daytime values.[13] A diminution (i.e., $< 10\%$) or reversal of this expected fall in blood pressure during the night has been labeled the "nondipping" pattern and, independent of the degree of hypertension, has been identified as a strong risk factor for cardiovascular target organ damage.[14,15] Importantly, patients with CKD, compared to individuals with normal renal function, are more likely

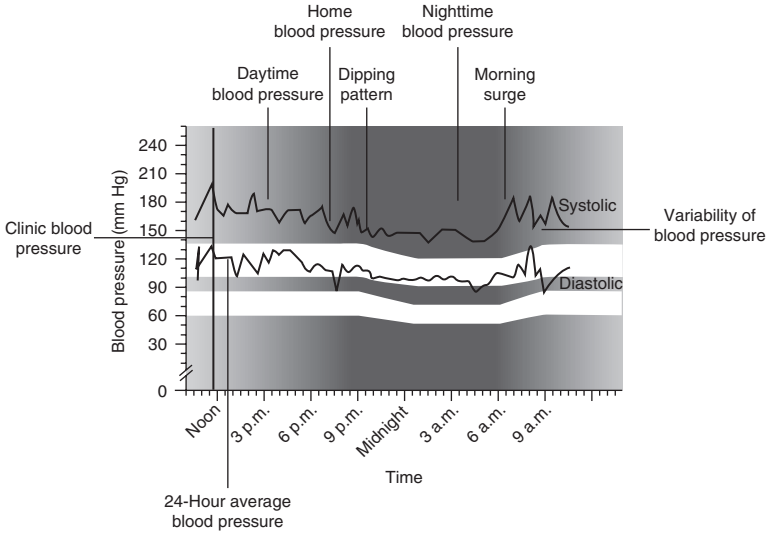

Figure 3.2. Twenty-four hour ambulatory blood pressure tracing in a patient with hypertension. The white zones represent the normal ranges of systolic and diastolic blood pressure.

Source: Adapted from Pickering TG, Shimbo D, Haas D. Ambulatory blood-pressure monitoring. *N Engl J Med.* 2006;354(22):2368–2374.

to be nondippers,[16] which may explain, in part, the higher rate of hypertensive complications in this diseased population.

Ambulatory blood pressure monitoring has consequently taken on a new and important role in properly assessing the diagnosis and treatment of hypertension in CKD. Data from post hoc analyses of the African American Study of Kidney Disease and Hypertension (AASK) clearly demonstrate that office blood pressures $< 130/80$ mm Hg did not ensure optimal slowing of kidney disease. Individuals with masked hypertension and/or nondipping hypertension had a much higher likelihood of disease progression in spite of adequately treated office blood pressure readings.[17] These differences in blood pressure over the time of day were also consistent with changes in left ventricular hypertrophy in the CKD population.[18] Additionally, data from Agarwal and colleagues indicate that ABPM on the day postdialysis provides the best measure of blood pressure control and a way to optimize blood pressure–lowering therapy for patients with end stage disease.[19–21] These varied uses of ABPM should be given strong consideration before assuming that blood pressure is well controlled in high risk CKD patients, as ABPM may

Table 3.1. Comparison of office, ambulatory, and self- (home) blood pressure monitoring

	Office BP	Ambulatory BP	Home BP
Predicts cardiovascular events	Yes	Yes	Yes
Diagnostic utility	Yes	Yes	Yes
Detects white coat hypertension	No	Yes	Yes
Detects masked hypertension	No	Yes	Yes
Evaluates BP circadian rhythm	No	Yes	No
Evaluates nocturnal BP	No	Yes	No
Evaluates therapy	Yes	Yes	Yes
Cost	Low	High	Low
Normal limit for average-risk patients	140/90 mm Hg	130/80 mm Hg (24 hour) 135/85 mm Hg (awake) 120/75 mm Hg (asleep)	135/85 mm Hg

Source: Adapted from Pickering TG, White WB. ASH position paper: Home and ambulatory blood pressure monitoring. When and how to use self (home) and ambulatory blood pressure monitoring. *J Clin Hypertens (Greenwich)*. 2008;10(11):850–855.

allow further adjustments to antihypertensive regimens that maximize control of pressure and thereby slow nephropathy progression and reduce cardiovascular risk.

GLOMERULAR FILTRATION RATE

CKD is defined as structural or functional abnormalities of the kidney that persist for at least 3 months and are manifested by kidney damage, most frequently detected as abnormal urinary albumin excretion (discussed later), or a below-60 ml/min/1.73 m^2 GFR.[22] While the most accurate method of evaluating kidney function is a formal GFR measurement with iothalamate, iohexol, or similar markers, these tests are too expensive and time consuming to be recommended for routine clinical practice. Currently, the most common methods used to estimate GFR are the serum creatinine concentration, calculated creatinine clearance, and estimation equations based upon serum creatinine.

Serum creatinine is a suitable indicator of GFR in patients with normal kidney function or chronic kidney disease provided that kidney function is essentially stable. Problems with the routine use of serum creatinine alone to infer GFR stem from the differing rates of creatinine production between individuals, mainly because of variations in muscle mass. Thus women and the elderly can have deceptively low serum creatinine levels despite significant

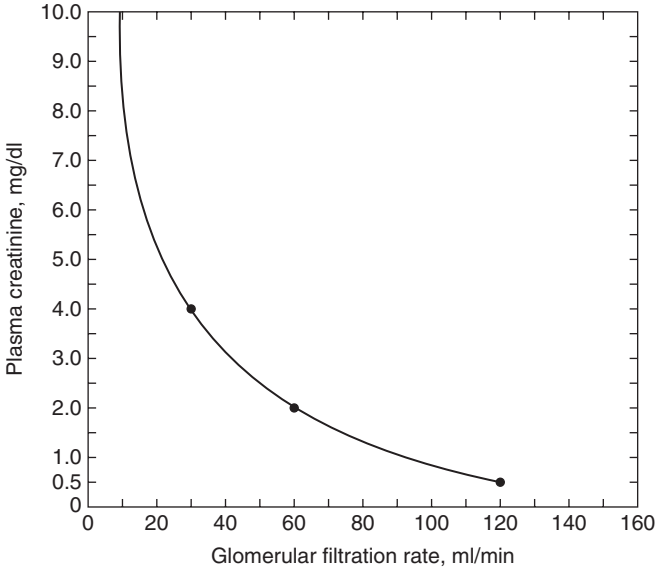

Figure 3.3. Relationship between plasma creatinine and GFR measured by inulin clearance.

Source: Adapted from Shemesh O, Golbetz H, Kriss JP, Myers BD. Limitations of creatinine as a filtration marker in glomerulopathic patients. *Kidney Int.* 1985;28(5):830–838.

declines in GFR. In addition, the shape of the curve relating the GFR to serum creatinine (**Figure 3.3**)[23] has an important and potentially easily overlooked clinical implication, namely that an initial small rise in creatinine usually reflects a marked fall in GFR. Calculation of creatinine clearance from a timed (typically 24-hour) urine collection can provide a more accurate estimation of GFR but is cumbersome and ripe for error due to inaccurate urine collection.

Therefore, several estimation equations for GFR that use easily obtained clinical data and laboratory results have been developed to allow healthcare providers to diagnose CKD with improved accuracy. To date, the most widely used equations are the Cockcroft-Gault[24] and Modification of Diet in Renal Disease (MDRD) study[25,26] equations, although a new equation developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI equation)[27] could emerge as the preferred formula for routine clinical use (**Table 3.2**). Weight estimations or ideal weight estimations can make calculation and reporting of Cockcroft-Gault results problematic. The MDRD equations (both the full and abbreviated forms) use

Table 3.2. Equations for estimating glomerular filtration rate (GFR)

Cockcroft-Gault	
Male	$\text{CCr (ml/min)} = \dfrac{(140 - \text{age}) \times \text{lean body wt (kg)}}{\text{SCr (mg/dl)} \times 72}$
Female	$\text{CCr (ml/min)} = \dfrac{(140 - \text{age}) \times \text{lean body wt (kg)} \times 0.85}{\text{SCr (mg/dl)} \times 72}$
MDRD 1	
Black male	$\text{GFR} = 170 \times \text{SCr}^{-0.999} \times \text{age}^{-0.176} \times \text{BUN}^{-0.170} \times \text{Albumin}^{0.318} \times 1.18$
Black female	$\text{GFR} = 170 \times \text{SCr}^{-0.999} \times \text{age}^{-0.176} \times \text{BUN}^{-0.170} \times \text{Albumin}^{0.318} \times 1.18 \times 0.762$
White male	$\text{GFR} = 170 \times \text{SCr}^{-0.999} \times \text{age}^{-0.176} \times \text{BUN}^{-0.170} \times \text{Albumin}^{0.318}$
White female	$\text{GFR} = 170 \times \text{SCr}^{-0.999} \times \text{age}^{-0.176} \times \text{BUN}^{-0.170} \times \text{Albumin}^{0.318} \times 0.762$
MDRD 2 (abbreviated)	
Black male	$\text{GFR} = 186 \times \text{SCr}^{-1.154} \times \text{age}^{-0.203} \times 1.21$
Black female	$\text{GFR} = 186 \times \text{SCr}^{-1.154} \times \text{age}^{-0.203} \times 1.21 \times 0.742$
White male	$\text{GFR} = 186 \times \text{SCr}^{-1.154} \times \text{age}^{-0.203}$
White female	$\text{GFR} = 186 \times \text{SCr}^{-1.154} \times \text{age}^{-0.203} \times 0.742$
CKD-EPI	
Black male, SCr $\leq$ 0.9 mg/dl	$\text{GFR} = 163 \times (\text{SCr}/0.9)^{-0.411} \times 0.993^{\text{age}}$
Black male, SCr $>$ 0.9 mg/dl	$\text{GFR} = 163 \times (\text{SCr}/0.9)^{-1.209} \times 0.993^{\text{age}}$
Black female, SCr $\leq$ 0.7 mg/dl	$\text{GFR} = 166 \times (\text{SCr}/0.7)^{-0.329} \times 0.993^{\text{age}}$
Black female, SCr $>$ 0.7 mg/dl	$\text{GFR} = 166 \times (\text{SCr}/0.7)^{-1.209} \times 0.993^{\text{age}}$
White male, SCr $\leq$ 0.9 mg/dl	$\text{GFR} = 141 \times (\text{SCr}/0.9)^{-0.411} \times 0.993^{\text{age}}$
White male, SCr $>$ 0.9 mg/dl	$\text{GFR} = 141 \times (\text{SCr}/0.9)^{-1.209} \times 0.993^{\text{age}}$
White female, SCr $\leq$ 0.7 mg/dl	$\text{GFR} = 144 \times (\text{SCr}/0.7)^{-0.329} \times 0.993^{\text{age}}$
White female, SCr $>$ 0.7 mg/dl	$\text{GFR} = 144 \times (\text{SCr}/0.7)^{-1.209} \times 0.993^{\text{age}}$

SCr, serum creatinine.

data that are readily available to laboratories, allowing routine reporting of estimated GFR alongside serum creatinine.[28] Yet the equations are imprecise and systematically underestimate GFR at higher values,[29] raising concern for false diagnoses of chronic kidney disease.[30–32]

The CKD-EPI equation, published in 2009 and developed by many of the same investigators who worked on the MDRD equation, appears to be more precise and accurate than the MDRD equation, especially at higher GFRs.[27] Further evaluation of the CKD-EPI equation—particularly among elderly and nonwhite individuals who were underrepresented in the sample used to develop the formulas—is needed before it replaces the MDRD equation, however. Guidelines from the National Kidney Foundation, American Heart Association, the American and European Societies of Hypertension, and a host of other organizations still recommend screening for kidney disease by measuring serum creatinine and calculating estimated GFR with the MDRD study equation.[22,33–35] If the estimated GFR is < 60 ml/min/1.73 m^2, then repeat testing should be performed in 3 months (or sooner if clinically indicated) to confirm a chronic reduction in kidney function.

Cystatin C, a serine protease inhibitor released at a relatively constant rate from all cells and freely filtered by the glomerulus without reabsorption, has recently emerged as a potentially better approximation of GFR than creatinine.[36–41] Cystatin C, unlike serum creatinine, was presumed to be unaffected by gender, age, or muscle mass, suggesting that this measurement (or a GFR-estimating equation based on this measurement) would be more accurate in populations with lower creatinine production, such as the elderly, children, and renal transplant recipients.[40,42–44] However, higher cystatin C levels have now been associated with male gender, greater height and weight, higher lean body mass, and advanced age.[45,46] Although reference ranges for cystatin C have been reported,[47] testing for cystatin C is only available in a limited number of laboratories at a far higher cost than serum creatinine. Therefore, its use remains limited to research settings at present.

ALBUMINURIA

The gold standard for measuring urinary albumin excretion is via a 24-hour urine collection, but because this is a cumbersome process that is prone to measurement error, the urine albumin-to-creatinine ratio (UACR) has emerged as a valid, easily obtained surrogate (mg albumin/g creatinine approximating mg albumin/day).[48] The UACR should preferably be measured in a first morning void, which has been shown to be more reliable than random urine samples for diagnosing and monitoring albuminuria,[49] although guidelines are still written for spot urine samples. The urine dipstick, by comparison, is considered an insensitive marker for proteinuria, not becoming positive until protein excretion exceeds, on average, 300–500 mg/day.

The normal rate of urinary albumin excretion is less than 20 mg/day. Persistent albumin excretion between 30 and 300 mg/day (20–200 μg/min) is termed microalbuminuria, while albumin excretion above 300 mg/day is considered overt proteinuria (i.e., detectable by dipstick) or macroalbuminuria. Gender-specific definitions for microalbuminuria have also been suggested—UACR 17–250 mg/g for men and 25–355 mg/g for women.[50] Spot UACR values above 30 mg/g are considered abnormal if persistent for more than 3 months. Microalbuminuria is a marker of endothelial dysfunction and an independent risk factor for cardiovascular events.[51–53] Repeated elevations of the UACR in the microalbuminuria range suggest but do

not definitively indicate kidney disease, as increased urinary albumin excretion may solely reflect generalized endothelial dysfunction.[54–58] However, because CKD and endothelial dysfunction are both associated with increased cardiovascular risk, screening for albuminuria should be routinely performed for all patients with hypertension. Indeed, in a post hoc analysis of the Losartan Intervention for Endpoint study, an early reduction in microalbuminuria was associated with a greater reduction in cardiovascular events that persisted over 5 years of follow-up (**Figure 3.4**).[59]

Macroalbuminuria or overt proteinuria, defined as sustained albumin excretion greater than 300 mg/day (or UACR > 300 mg/g), is associated with a much higher cardiovascular risk and clearly indicates presence of kidney disease.[60] A direct relationship exists between the degree of proteinuria and risk of progression to end stage renal disease. Post hoc analyses of 3 appropriately powered CKD outcomes trials—the Irbesartan in Diabetic Nephropathy Trial (IDNT),[61] the Reduction of Endpoints in Non-insulin Dependent Diabetes Mellitus with the

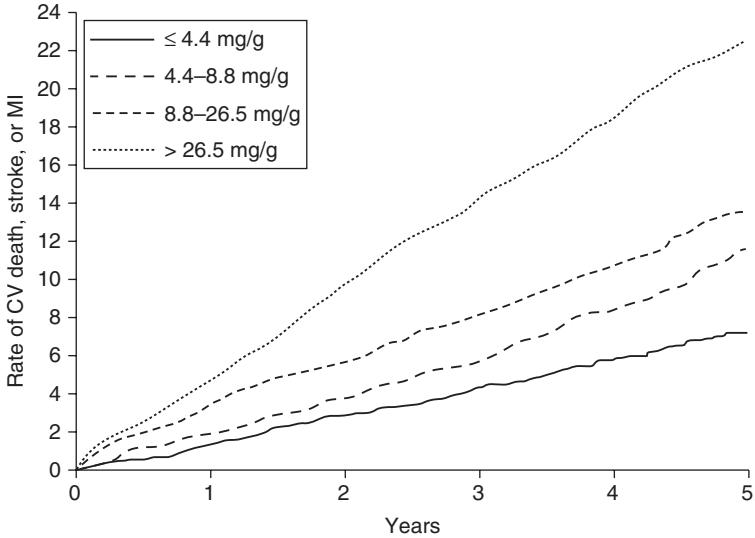

Figure 3.4. Composite end point in the LIFE study, stratified by time-varying measures of albuminuria.

Source: Adapted from Ibsen H, Olsen MH, Wachtell K, et al. Reduction in albuminuria translates to reduction in cardiovascular events in hypertensive patients: losartan intervention for endpoint reduction in hypertension study. *Hypertension.* 2005;45(2):198–202.

Table 3.3. Outcomes studies with primary CKD progression end point in which post hoc analyses showed significant risk reduction for CKD progression with proteinuria reduction

Study	Treatment Groups	Mean Follow-up	Change in Proteinuria	Relevant Outcomes
AASK	Ramipril, metoprolol, or amlodipine with conventional or intensive blood pressure targets	4 years	−20% for ramipril −14% for metoprolol +58% for amlodipine[a]	Ramipril slowed the progression of renal disease more than the other groups
RENAAL	Losartan or placebo	3.4 years	−39% for losartan −5% for placebo[b]	Losartan delayed the need for dialysis by 2 years; placebo did not
IDNT	Irbesartan, amlodipine, or placebo	2.6 years	−41% for irbesartan −11% for amlodipine −16% for placebob	Irbesartan reduced proteinuria to a greater extent and led to slower progression of renal disease than the other groups

[a] At 6 months.
[b] At 12 months.

Angiotensin II Antagonist Losartan (RENAAL) trial,[62] and the AASK trial[63]—have demonstrated that a reduction in proteinuria, independent of blood pressure reduction, delays progression of kidney disease. Specifically, these studies demonstrated that a reduction in proteinuria of more than 30% resulted in a roughly 40–70% risk reduction for end stage renal disease over 3–5 years (**Table 3.3**). Nonetheless, to date there is no randomized prospective trial demonstrating that a change in albuminuria alters CKD progression independent of blood pressure reduction, and therefore albuminuria does not currently qualify as a surrogate marker according to the Food and Drug Administration.[64]

Despite the aforementioned uncertainties about both GFR estimating equations and whether microalbuminuria truly indicates kidney disease, both the National Kidney Foundation and American Heart Association recommend combined screening for microalbuminuria and estimated GFR with the MDRD study equation for all adult patients with cardiovascular disease as well as those with risk factors for CKD, such as diabetes, hypertension, family history of kidney disease, and obesity (which are also risk factors for cardiovascular disease). Repeat screening should be performed at 3 months if either test is positive, and if either test remains positive over at least a 3-month period, the patient should be considered to have CKD. Appropriate further evaluation as to the cause of CKD—including imaging studies, microscopic urinalysis, and referral to a nephrologist—along with initiation of appropriate treatment should be undertaken to slow or halt progression of kidney disease. A hallmark of this appropriate treatment is effective antihypertensive therapies,[22,33,34] which will be taken up in later chapters.

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Chapter 4

Secondary and Resistant Hypertension

Secondary hypertension is the term used to describe elevated blood pressure in the setting of an identifiable, underlying, etiologic condition (**Table 4.1**). In those individuals without a clear underlying etiology for elevated blood pressure, the term *primary* or *essential* hypertension is used. This is likely a misnomer. An individual presenting in his mid-40s with elevated blood pressure may be diagnosed with essential hypertension despite a strong family history of hypertension suggesting an inherent, genetic predisposition. Therefore, with advances in our understanding of epidemiology, genetics, and pathophysiology, it is conceivable that we will someday be able to identify the cause (or causes) of hypertension for all patients and the terms *primary* and *secondary* hypertension will fall out of use.

Secondary hypertension should be considered in patients with severe hypertension (systolic blood pressure above 170 mm Hg or diastolic blood pressure above 110 mm Hg), chronically difficult-to-control hypertension, or an acute rise in blood pressure over previously well-controlled values. In addition, patients who develop hypertension before puberty should always be screened for secondary causes of hypertension, as should nonobese patients without a confirmed family history of hypertension who present before age 30 with elevated blood pressure. If an etiology is discovered and secondary hypertension diagnosed, it is presumed that resolution of the underlying etiology (e.g., surgical treatment of a pheochromocytoma) will normalize blood pressure, which may or may not always occur. For example, most young women who undergo correction of fibromuscular dysplasia in a timely fashion will experience normalization of their blood pressure, whereas middle-aged individuals who begin nightly continuous positive airway pressure (CPAP) therapy for obstructive sleep apnea may only see small, but still significant, drops in blood pressure that result in a reduction, but not elimination, of antihypertensive medications.

In this chapter, we will focus on the related concept of resistant hypertension, which is defined by a blood pressure of at least 140/90 mm Hg or at least 130/80 mm Hg in patients

Table 4.1. Causes of secondary hypertension

Renal parenchymal disease
Renovascular disease
Hyperaldosteronism
Thyroid disease
Pheochromocytoma
Oral contraceptives
Obstructive sleep apnea
Coarctation of the aorta
Cushing's syndrome
Primary hyperparathyroidism

Source: Adapted from Sarafidis PA, Bakris GL. Resistant hypertension: an overview of evaluation and treatment. *J Am Coll Cardiol*. 2008;52(22):1749–1757.

Table 4.2. Causes of pseudo-resistant hypertension

Cause	Example
Improper blood pressure measurement	Inappropriately sized cuff
White-coat hypertension	Persistently lower home blood pressures
Difficult to compress heavily calcified or sclerotic arteries	Very elderly patients
Poor patient adherence	Complicated dosing schedules, high costs of medications
Inadequate antihypertensive medication	Inappropriate combinations, insufficient doses
Physician inertia	Failure to change or increase dose regimens

Source: Adapted from Sarafidis PA, Bakris GL. Resistant hypertension: an overview of evaluation and treatment. *J Am Coll Cardiol*. 2008;52(22):1749–1757.

with diabetes or chronic kidney disease (CKD) despite adherence to treatment with full doses of at least 3 antihypertensive medications, including a diuretic.[1] The causes of resistant hypertension are essentially the same as those of secondary hypertension. Yet while secondary hypertension is generally considered a rare entity, resistant hypertension is an increasingly recognized clinical phenomenon, occurring in up to 40% of hypertensive patients.[2,3]

The concept of resistant hypertension, akin to the concept of secondary hypertension, is focused on identifying patients who are at high risk of having reversible causes of hypertension and who, because of persistently elevated blood pressure, may benefit from special diagnostic or therapeutic considerations. Pseudoresistant hypertension should first be distinguished from true resistant hypertension. Pseudoresistance refers to lack of blood pressure control with appropriate treatment in a patient who does not have truly resistant hypertension. A number of factors can contribute to elevated blood pressure readings and simulate resistant hypertension, including poor blood pressure measurement technique, white-coat hypertension, and patient noncompliance with prescribed therapy and diet (**Table 4.2**). If such factors are effectively ruled out, then a more thorough investigation into the causes of true resistant hypertension should be pursued (**Table 4.3**).

CHRONIC KIDNEY DISEASE

The prevalence of resistant hypertension likely falls in the 5–15% range in general medical practices but rises to more than 50% in nephrology clinics.[4] The kidney clearly plays a crucial role in the genesis of hypertension as well as the response to antihypertensive treatment. Arthur Guyton's seminal pressure-natriuresis theory points to the renal handling of sodium as the ultimate determinant of blood pressure.[5–9] Individuals with normal renal function are able to effectively excrete their sodium loads, but individuals with impaired renal function must raise their blood pressures to efficiently excrete sodium and stay in steady state. Thus, a functional abnormality in the kidney is considered a fundamental condition for the development of hypertension.

Table 4.3. Factors contributing to resistant hypertension

Drug-induced
Nonsteroidal anti-inflammatory drugs
Sympathomimetics (e.g., decongestants, anorectics)
Cocaine
Amphetamines
Oral contraceptives
Calcineurin inhibitors
Erythropoiesis-stimulating agents
Licorice
Dietary and herbal supplements (e.g., ginseng, yohimbine)
Excessive alcohol intake
Hypervolemia
High dietary sodium intake
Inadequate diuretic therapy
Volume retention from impaired kidney function
Associated conditions
Obesity
Diabetes mellitus
Advanced age
Identifiable/secondary causes of hypertension
Pheochromocytoma
Renal parenchymal disease
Renovascular disease
Hyperaldosteronism
Obstructive sleep apnea
Cushing's syndrome
Thyroid diseases
Coarctation of the aorta
Intracranial tumors

Source: Adapted from Sarafidis PA, Bakris GL. Resistant hypertension: an overview of evaluation and treatment. *J Am Coll Cardiol*. 2008;52(22):1749–1757.

A number of studies in animals and humans have shown that blood pressure follows kidney function, encapsulated in the saying, "Blood pressure goes with the kidney."[10] Transplantation of a kidney from a genetically hypertension-prone donor rat caused progressive increase of blood pressure in a normotensive recipient; conversely, kidneys from normotensive donors lowered blood pressure in spontaneously hypertensive rat recipients.[11–13] This phenomenon has also been observed in human kidney transplant recipients. Recipients of kidneys from donors dying from cerebral hemorrhage, presumably in the setting of hypertension, had a higher risk to develop hypertension,[14] whereas a number of patients with hypertension-induced end stage renal disease have become normotensive after transplantation.[15] Other

evidence for the critical role of kidney function in the development of hypertension comes from epidemiologic studies. For example, in the Multi-Ethnic Study of Atherosclerosis, 2767 participants without hypertension or clinically recognized kidney disease were followed for a median of 3.1 years, during which 545 participants (20%) developed hypertension. After adjustment for established hypertension risk factors, each 15 nmol/L increase in cystatin C (a potentially more sensitive measure of kidney function than serum creatinine, discussed in Chapter 3) was associated with a 15% greater incidence of hypertension.[16]

A number of factors other than impaired sodium handling may contribute to the pathogenesis of hypertension in individuals with CKD, including increased activity of the renin-angiotensin-aldosterone system, enhanced sympathetic activity, and impaired nitric oxide synthesis and endothelium-mediated vasodilatation.[17–19] Additionally, two common complications of CKD, anemia and secondary hyperparathyroidism, can exacerbate hypertension. Correction of anemia with erythropoiesis-stimulating agents has been shown to raise blood pressure; while this effect was felt originally to be related to the degree of elevation in hematocrit, more recent analyses suggest that erythropoiesis-stimulating agents increase blood pressure directly and independently of their erythropoietic effect.[20] Secondary hyperparathyroidism raises intracellular calcium concentrations, which can lead to vasoconstriction and subsequent blood pressure elevation.[21] In light of the pathologic mechanisms of hypertension, patients with CKD and hypertension should be prescribed—in addition to a low-salt diet usually alongside a diuretic—renin-angiotensin system blocking drugs, vitamin D or vitamin D analogs if parathyroid hormone levels are elevated, and the lowest possible doses of erythropoiesis-stimulating agents if anemia warrants correction.

Blood pressure is also often elevated in cases of acute (as opposed to chronic) kidney injury. This is particularly true in acute glomerular diseases, such as postinfectious glomerulonephritides, focal segmental glomerulosclerosis, minimal change disease, membranous nephropathy, and rapidly progressive glomerulonephritis (e.g., lupus-associated or anti-neutrophil cytoplasmic antibody [ANCA]–associated). Patients with acute glomerulopathies are often volume expanded and edematous. This fluid overload should lead to a compensatory, enhanced release of atrial natriuretic peptide to enact sodium excretion and normalization of volume status, but a relative resistance to atrial natriuretic peptide in the collecting tubules occurs in acute glomerular diseases.[22,23] In addition, acute glomerular injury stimulates activity of the Na-K-ATPase pump in the collecting tubule to actively transport sodium back into the circulation.[24] The end result is marked sodium retention, further volume expansion, and subsequent elevations in blood pressure.

Acute vascular diseases of the kidney, such as systemic vasculitides, thrombotic microangiopathies, and scleroderma, also are associated with significant blood pressure rises. The pathophysiology here is felt to be due to ischemic injury to the renal parenchyma with consequent overactivation of the renin-angiotensin system. Because the other previously mentioned salt-retaining mechanisms are not stimulated, such vascular insults to the kidney, at least in the acute phase, are not marked by volume expansion and edema. This may help clinically in differentiating acute glomerulonephritis, typically an edematous state, from acute primary vascular disease, a generally nonedematous state. The distinction also extends to treatment decisions. In scleroderma renal crisis, for example, initiation of prompt renin-angiotensin system blockade with an angiotensin-converting enzyme (ACE) inhibitor is a mandatory step (and, sometimes, the only step needed) for controlling blood pressure,[25–27] while patients with

acute glomerulonephritides typically will require diuretic therapy in the acute phase to manage their hypertension and edema.

Given the crucial role of the kidney in the pathogenesis of hypertension, any patient presenting with new-onset hypertension should be evaluated for acute and/or chronic kidney disease.[1,28] This assessment of kidney function should include, at a minimum, testing for serum creatinine (with estimation of glomerular filtration rate) and abnormal urinary albumin excretion. Ultrasound evaluation of the kidney, microscopic analysis of the urinary sediment, 24-hour urine collection for proteinuria and creatinine clearance, an extensive serologic work-up for systemic causes of glomerular diseases (e.g., testing for antinuclear antibodies, ANCA, hepatitis B and C), and, in some cases, a renal biopsy may also be needed to diagnose the cause of kidney disease and, consequently, the cause of hypertension. The treatment of hypertension in kidney disease, as discussed in Chapter 6, will usually involve a renin-angiotensin system blocking drug and a diuretic, and often 1 or 2 more agents, but the cause of kidney disease should be considered in choosing therapy.

RENAL ARTERY DISEASE

Renovascular hypertension is defined as elevated blood pressure resulting from renal arterial compromise, often due to occlusive lesions in the main renal arteries.[29,30] If systemic hypertension is related directly to an arterial lesion, then relief of the obstruction, presumably, should lead to reversal of the hypertension. Yet this complete reversal of hypertension is only rarely achieved. Renovascular disease is less likely to *cause* hypertension than to accelerate or impair control of preexisting hypertension; in other words, renovascular hypertension is far more likely to present as resistant rather than secondary hypertension. Renovascular lesions also can threaten the viability of the poststenotic kidney and impair sodium excretion in patients with congestive heart failure. Thus, blood pressure control (rather than reversal), preservation or salvage of kidney function, and prevention of flash pulmonary edema may be important treatment goals for patients with renal arterial compromise.

Atherosclerosis accounts for approximately 90% of cases of renal artery stenosis and is increasingly common in aging populations. Diabetes, hyperlipidemia, aortoiliac occlusive disease, coronary artery disease, and hypertension all increase the risk for renovascular atherosclerotic lesions, again particularly so in elderly patients.[31] The prevalence of atherosclerotic renal artery stenosis is poorly defined but may rise as high as 30% among patients with coronary artery disease and to 50% among elderly people or individuals with diffuse atherosclerotic vascular diseases.[32,33] At least 10% of patients with end stage kidney disease requiring dialysis have been found to have atherosclerotic renal artery stenosis, and the disease burden is likely much higher.[34,35]

Atherosclerotic renal artery stenosis is a progressive disease that usually is accompanied by hypertension and may also coincide with ischemic kidney disease.[31] Yet the presence of vascular lesion(s) does not necessarily translate to the lesion(s) being responsible for blood pressure elevations or renal dysfunction. The last 3 decades have seen major advances in vascular imaging techniques, particularly in noninvasive imaging modalities such as ultrasound duplex and magnetic resonance (MR) angiography, which has led to a higher rate of diagnoses

(and, in many instances, attempts at correction) of atherosclerotic renovascular disease. In this same time period, however, similar advances have been made in the pharmacologic treatments of hypertension, hyperlipidemia, and diabetes, thereby allowing more effective medical management options for renovascular lesions. The outcomes from small, prospective trials, when pooled, have failed to establish major morbidity or mortality benefits of revascularization performed either by endovascular procedures (angioplasty or stent placement) or surgery compared to optimized medication regimens.[36]

In light of what was deemed a true state of equipoise between medical therapy and renal revascularization, the National Institutes of Health sponsored a large, multicenter, randomized clinical trial comparing intensive medical therapy alone to intensive therapy plus revascularization. The Cardiovascular Outcomes for Renal Atherosclerotic Lesions trial enrolled over 1000 patients with atherosclerotic renal artery stenosis with at least 60% narrowing and systolic hypertension for which they were receiving 2 or more antihypertensive medications.[37] The results from this trial are expected to be reported in 2010. Results from a similar study based in the United Kingdom—the Angioplasty and Stenting in Renal Atherosclerotic Lesions trial[38]—were published in 2009 and reported substantial risks but no evidence of a worthwhile clinical benefit from revascularization in patients with atherosclerotic renovascular disease.[39] Among 806 patients with an average 76% stenotic occlusion of the renal arteries and entry serum creatinine above 2.0 mg/dl, randomized to medical therapy with or without stenting, no differences were detected regarding blood pressure control, kidney function, heart failure hospitalizations, or mortality over a median follow-up period exceeding 2 years. Serious complications associated with revascularization occurred in 23 patients, including 2 deaths and 3 amputations of toes or limbs.

While the Angioplasty and Stenting in Renal Atherosclerotic Lesions trial results suggest that revascularization imposes no benefit beyond medical therapy for cardiovascular and renal outcomes, nearly all treating nephrologists and cardiologists can cite cases when revascularization has yielded impressive results. These anecdotal successes likely can be explained by a brief discussion of the difference between renal artery stenosis—an anatomic descriptor—and true renovascular hypertension—a functional descriptor. Imaging modalities such as MR or computed tomography (CT) angiography, ultrasound examination, and intra-arterial angiography typically only provide an anatomic diagnosis of a renal arterial lesion. These techniques can identify that a lesion exists but cannot impart whether such a lesion is truly impacting a patient's blood pressure or kidney function.

Functional studies, however, can provide such information. Captopril renography remains, in most centers, the best modality to provide functional assessment of overall perfusion and function.[40] Oral captopril is given 1 hour before a marker of glomerular filtration such as diethylenetriaminepentaacetic acid is injected. The efficacy of this test is based upon the typical ACE inhibitor–induced decline in GFR in the stenotic kidney, often accompanied by an equivalent increase in GFR in the contralateral kidney, with the net effect that the difference between the 2 kidneys is enhanced. Unfortunately, this test can be unreliable when baseline kidney function is abnormal, as asymmetries in renal flow and function can be present for reasons other than renovascular disease.[30] A simpler, albeit less rigorous, test is to measure the rise in plasma renin activity (PRA) 1 hour after the administration of oral captopril.[41] Patients with a functional renal artery lesion should have an exaggerated increase in PRA, perhaps due to removal of the normal suppressive effect of high angiotensin II levels on renin secretion in

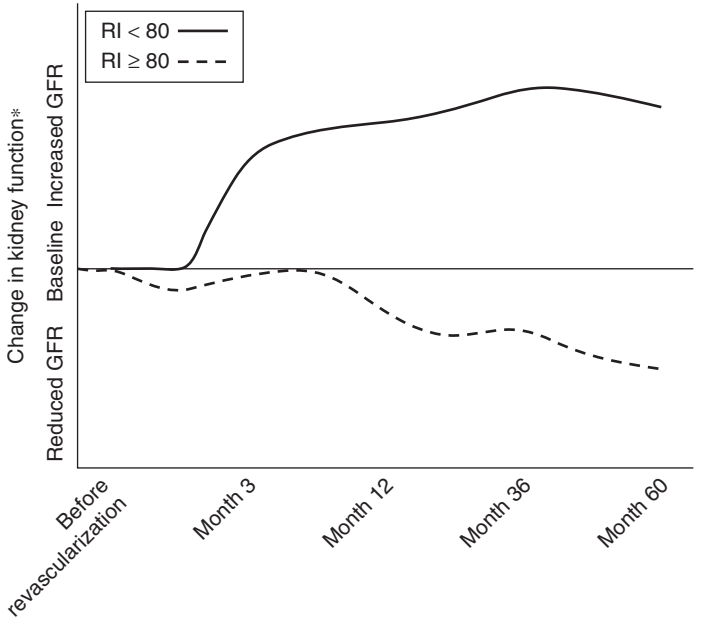
the stenotic kidney. Simple screening for elevated PRA (i.e., without stimulation) is not sufficient, as baseline PRA is elevated in only 50–80% of patients with renovascular disease.

Duplex Doppler ultrasonography can provide both anatomic and functional assessment of the renal arteries and, in centers with technical expertise in this modality, may emerge as the ideal screening tool for renovascular hypertension. Direct visualization of the main renal arteries (B-mode imaging) is combined with measurement (via Doppler) of a variety of hemodynamic factors. Radermacher et al. reported in 2001 on 131 patients who had unilateral or bilateral renal artery stenosis of more than 50% of the luminal diameter who underwent successful renal angioplasty or surgery. All patients were initially evaluated for stenosis using color Doppler ultrasonography including measurement of the resistance index (RI): [1—(end-diastolic velocity ÷ maximal systolic velocity)] × 100. Among the 35 patients who had RI values of 80 or higher before revascularization, the mean arterial pressure did not decrease by 10 mm Hg or more after revascularization in 34 (97%), renal function declined in 28 (80%), 16 (46%) became dependent on dialysis, and 10 (29%) died during follow-up. In contrast, among the 96 patients whose RI values were less than 80, the mean arterial pressure decreased by at least 10 percent in all but 6 patients (6%) after revascularization, renal function worsened in only 3 (3%), and 3 (3%) died (**Figure 4.1**).[42] Their conclusion that a renal RI value of 80 or higher identifies patients with renal artery stenosis in whom angioplasty or surgery will not improve renal function, blood pressure, or kidney survival has not been universally confirmed, however.[43–45]

Fibromuscular disease or dysplasia (FMD) is much rarer than atherosclerotic renal artery disease. Classically, this disease has been described as a cause of hypertension in younger females, sometimes first presenting during pregnancy. The prevalence of FMD drops markedly with age; among patients with renovascular hypertension, FMD accounts for up to 50% of cases in children but less than 15% of cases in adults.[46–48] Among adults, FMD is far more common among females, with a prevalence up to 10 times higher than among males. Only rarely does FMD lead to complete or segmental occlusion of the renal arteries, with most individuals presenting with normal kidney function but significantly elevated blood pressure. While duplex ultrasonography and MR angiography can make the diagnosis of FMD, renal arteriography should be the first diagnostic test for patients judged clinically to be at high risk for FMD-associated renovascular hypertension, as this imaging modality allows for simultaneous treatment with percutaneous transluminal angioplasty. Hypertension is usually cured or improved with angioplasty, but up to 30% of patients fail to manifest benefit after intervention.[47,49–51] The rate of restenosis following angioplasty ranges from 12% to 34% over follow-up intervals of 6 months to 2 years, but restenosis does not always lead to recurrent hypertension.[52]

ALDOSTERONE

Traditionally, aldosterone has been considered to be a hormone primarily involved in the regulation of extracellular volume and potassium homeostasis via its effects on epithelial cells primarily in the distal nephron and, to a far lesser degree, in the colon, salivary glands, and sweat glands. In this classic or epithelial pathway, aldosterone is produced in response to



*Kidney function assessed by creatinine clearance.

Figure 4.1. Mean changes in creatinine clearance after correction of renal artery stenosis, according to the resistance-index (RI) value before revascularization.

Source: Adapted from Radermacher J, Chavan A, Bleck J, et al. Use of Doppler ultrasonography to predict the outcome of therapy for renal-artery stenosis. *N Engl J Med.* 2001;344(6):410–417.

potassium, angiotensin II, and adrenocorticotrophic hormone and, upon binding to epithelial mineralocorticoid receptors, enacts sodium and water reabsorption alongside potassium and magnesium excretion (**Table 4.4**). If these epithelial mineralocorticoid receptors are overstimulated, as is the case in primary hyperaldosteronism from an aldosterone-producing adenoma or bilateral adrenal hyperplasia, or in much rarer diseases such as Liddle's syndrome or glucocorticoid remediable aldosteronism, blood pressure can be markedly elevated and often accompanied by hypokalemia and/or hypomagnesemia.

In recent years, however, a paradigm shift has occurred in our understanding of the widespread effects of aldosterone on *non*epithelial tissue in the heart, kidney, central nervous system, and vasculature. In this nonclassic, nonepithelial pathway, aldosterone activates

Table 4.4. The classic and nonclassic actions of aldosterone

Classic, Epithelial Pathway	Nonclassic, Nonepithelial Pathway
Aldosterone produced in response to AII, K, and ACTH	Aldosterone production is inappropriately elevated and not well modulated by volume status
Aldosterone binds to mineralocorticoid receptors in epithelial cells • Distal nephron • Colon • Salivary and sweat glands	Aldosterone binds to mineralocorticoid receptors in nonepithelial cells • Kidney • Heart • Vasculature
Aldosterone stimulates salt and water reabsorption	Aldosterone stimulates fibrosis
Aldosterone stimulates potassium excretion	Aldosterone stimulates oxidative stress and inflammation
End result is volume expansion and hypertension	End result is target organ damage in the kidney and heart

mineralocorticoid receptors in nonepithelial tissues of the heart, kidney, and peripheral vasculature to foster inflammation and fibrosis, a maladaptive response that typically occurs in normal to high salt states, when aldosterone levels should be suppressed.[53–58] These nonepithelial effects of aldosterone have sparked renewed interest in aldosterone blockade as therapy for chronic heart and kidney disease, including resistant hypertension.

Interruption of the renin angiotensin aldosterone system (RAAS) with ACE inhibitors or angiotensin receptor blockers (ARBs) remains the cornerstone of antihypertensive therapy in patients with evidence of end-organ damage in the heart and kidney.[59–63] Nevertheless, many individuals manifest progressive disease despite treatment, prompting speculation that ACE inhibitors and ARBs, for these patients, do not adequately target the aldosterone component of the RAAS.[64–66] In clinical trials of ACE inhibitors and ARBs, plasma aldosterone levels, after an initial decline, have been shown to increase in 30–50% of patients during the first year of therapy (**Table 4.5**).[67] This phenomenon, termed *aldosterone escape* or *aldosterone breakthrough*, likely carries important clinical consequences given the hormone's nonepithelial, profibrotic actions on the heart and kidney.[53,68–71] For example, aldosterone escape has been linked to left ventricular hypertrophy,[72] increased urinary albumin excretion,[73,74] steeper decline in estimated GFR,[64] and impaired exercise tolerance.[75] This relative or refractory hyperaldosteronism[76] may also be the root of resistant hypertension for a substantial number of patients.

Historically, excess aldosteronism was thought to be an uncommon cause of hypertension, but as assays for aldosterone and plasma renin activity have become widely available, and the aldosterone-to-renin ratio has emerged as a potential screening test for hyperaldosteronism, the prevalence of hyperaldosteronism has markedly risen. Whereas older medical textbooks have placed the prevalence of primary aldosteronism at less than 1% among general hypertensive patients, studies in the last 2 decades have demonstrated a prevalence that approaches 20–25% among hypertensive patients seen in specialty clinics.[56] Using the blood

Table 4.5. Incidence of aldosterone breakthrough

Study	Subjects	CHF	CKD	RAAS Blockade	Definition of Aldosterone Breakthrough	Incidence of Aldosterone Breakthrough
Lee et al., 1999[77]	22	Yes	No	ACE-I (titrated to maximum tolerated dose) for 18 months	Aldosterone > 80 pg/ml[a] after 18 months	23% (5/22)
MacFadyen et al, 1999[78]	91	Yes	No	Stable ACE-I therapy for at least 4 weeks	Aldosterone > 144 pg/ml[a] after at least 4 weeks	38% (35/91)
Sato and Saruta, 2001[72]	74	No	No	ACE-I for 40 weeks	Aldosterone ≥ baseline levels after 40 weeks	51% (38/75)
Cicoira et al, 2002[75]	141	Yes	No	ACE-I for at least 6 months	Aldosterone > 0.42 nmol/l[a] after at least 6 months	10% (14/141)
Tang et al, 2002[79]	75	Yes	No	Enalapril (randomized to 2.5 mg bid or 20 mg bid) for 6 months	Aldosterone ≥ 160 pg/ml[a] after 6 months	35% (26/75)
Sato et al, 2003[73]	45	No	Yes	ACE-I (trandolapril titrated to goal BP 130/85) for 40 weeks	Aldosterone ≥ baseline levels after 40 weeks	40% (18/40)
Schjoedt et al, 2004[64]	63	No	Yes	Losartan 100 mg qd for 24–42 months	Aldosterone ≥ baseline levels after 24–42 months	41% (26/63)
Horita et al, 2006[74]	43	No	Yes	Temocapril 1 mg qd, losartan 12.5 mg qd, or both for 12 months	Aldosterone ≥ baseline levels after 12 months	53% (23/43)

CHF, congestive heart failure; CKD, chronic kidney disease; RAAS, renin-angiotensin-aldosterone system; ACE-I, angiotensin-converting enzyme inhibitor; BP, blood pressure.

[a] In normal subjects with normal sodium intake, values for plasma aldosterone range from 50 to 150 pg/ml (0.139 to 0.416 nmol/l).

Source: Adapted from Bomback AS, Klemmer PJ. The incidence and implications of aldosterone breakthrough. *Nat Clin Pract Nephrol*. 2007;3(9):486–492.

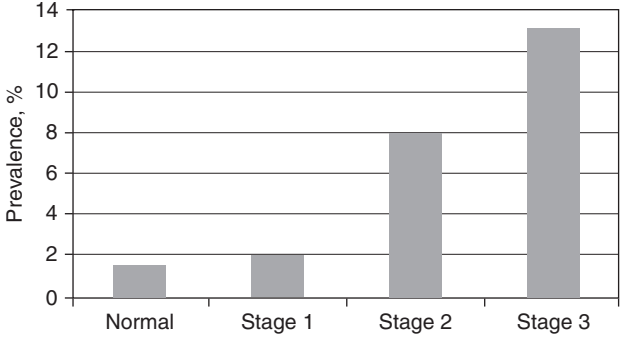


Figure 4.2. Prevalence (%) of primary aldosteronism according to hypertension stage (JNC VI classification) in 609 essential hypertensive patients.

Source: Adapted from Mosso L, Carvajal C, Gonzalez A, et al. Primary aldosteronism and hypertensive disease. *Hypertension.* 2003;42(2):161–165.

pressure classifications from the Joint National Committee 6 (*JNC 6*)—stage 1, SBP 140–159, DBP 90-99; stage 2, SBP 160-179, DBP 100-109; and stage 3, SBP > 180, DBP > 110 mm Hg—Mosso and colleagues demonstrated that the prevalence of primary aldosteronism (confirmed by fludrocortisone suppression test) rose exponentially as blood pressure rose higher, from 2% in stage 1 hypertension to 13% in stage 3 hypertension (**Figure 4.2**).[80] Even aldosterone levels presumed to be in normal range can contribute to hypertension, as reported in the Framingham Offspring Cohort Study. A group of 1688 nonhypertensive individuals with a mean age of 55 years were followed for approximately 4 years and broken into quartiles of aldosterone levels, from lowest to highest, but still within the range of normal aldosterone levels. Age- and sex-adjusted analyses demonstrated a clear linear pattern between aldosterone levels and progression to overt hypertension, defined as a systolic blood pressure of 140 mm Hg or higher, a diastolic blood pressure of 90 mm Hg or higher, or the use of antihypertensive medications (**Figure 4.3**).[81]

Perhaps not surprisingly, aldosterone blockade has emerged as an effective treatment strategy for resistant hypertension (**Figure 4.4**). The strongest evidence comes from the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), in which 1411 participants received spironolactone as a fourth-line antihypertensive agent for uncontrolled blood pressure. Spironolactone therapy (median dose 25 mg/day, median duration of treatment 1.3 years) led to a mean decrease in systolic blood pressure of 21.8 mm Hg (156.9 to 135.1) and diastolic blood pressure of 9.5 mm Hg (85.3 to 75.8).[82] This marked effect may be due to the aldosterone escape phenomenon or the higher prevalence of primary aldosteronism in subjects with resistant hypertension. However, an earlier, smaller study found similar effects of low-dose spironolactone on resistant hypertension (a mean decrease in blood pressure of 25/12 mm Hg after 6 months of therapy) in subjects with *and* without primary aldosteronism.[83] Defining primary aldosteronism can be difficult in resistant hypertension if volume and salt status are

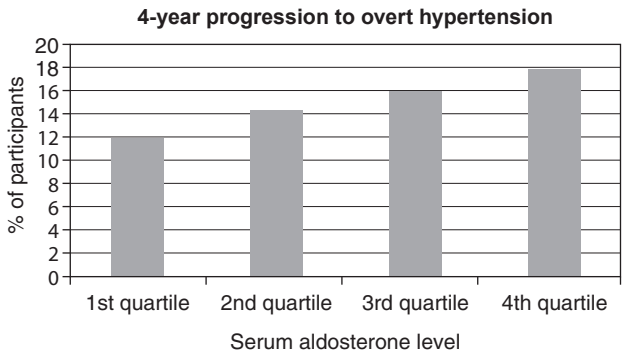


Figure 4.3. Age- and sex-adjusted rates of progression to overt hypertension according to quartile of serum aldosterone level among nonhypertensive subjects in the Framingham Offspring Cohort Study.

Source: Adapted from Vasan RS, Evans JC, Larson MG, et al. Serum aldosterone and the incidence of hypertension in nonhypertensive persons. *N Engl J Med.* 2004;351(1):33–41.

not accounted for, and normal aldosterone levels in patients with resistant hypertension may be pathologic given the volume expansion commonly seen in this disease state.[84]

In patients with resistant hypertension, aldosterone blockade may take on increased importance not only to achieve better control of blood pressure but also to protect against the nonepithelial effects of aldosterone. Most of the patients enrolled in the landmark congestive heart failure trials of spironolactone (the Randomized Aldactone Evaluation Study, RALES)[85] and eplerenone (the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study, EPHESUS),[86] in which aldosterone blockade reduced all-cause mortality, met criteria for resistant hypertension. Similarly, in the handful of small CKD trials in which aldosterone blockade, added to ACE inhibitors and/or ARBs, significantly reduced proteinuria by 30–40%,[87,88] nearly all participants would be categorized as having resistant hypertension. A recent, placebo-controlled trial in 112 patients with stage 2 and 3 CKD on established ACE inhibitor or ARB treatment alongside other antihypertensive agents found that, compared with placebo, spironolactone (25 mg daily) significantly improved left ventricular mass and measures of arterial stiffness (pulse wave velocity, augmentation index, and aortic distensibility).[89]

The role for aldosterone antagonists in patients with resistant hypertension, congestive heart failure, and chronic kidney disease clearly has grown, which, in turn, has led to an increased concern regarding the risk for hyperkalemia that can accompany these drugs. After publication of the RALES, for example, a study from Ontario reported that spironolactone prescriptions for patients treated with ACE inhibitors hospitalized for heart failure rose by a factor of 5; as a result, there were more than 500 additional hyperkalemia-related hospitalizations

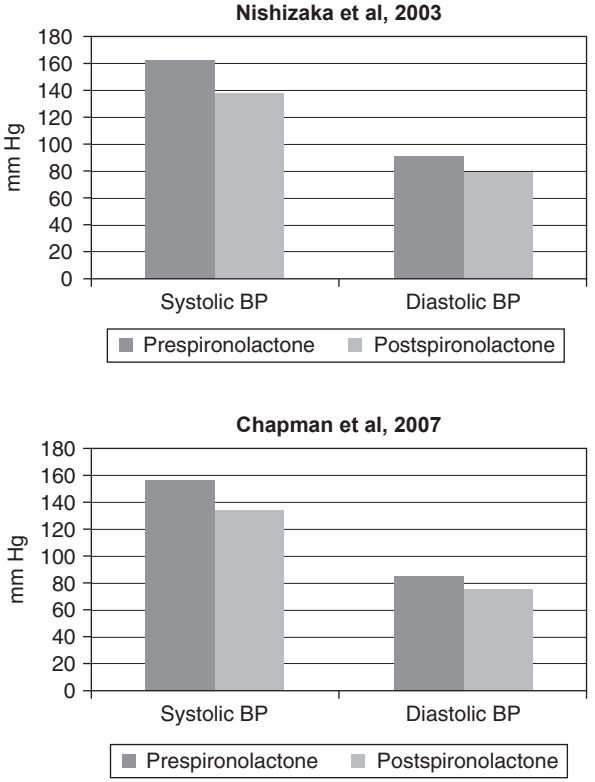


Figure 4.4. Low-dose spironolactone (12.5–25 mg/day) induced reductions in systolic and diastolic blood pressure in two studies of resistant hypertension. Nishizaka et al. (2003) reported on 76 subjects with resistant hypertension; Chapman et al. (2007) reported on 1411 subjects.

Source: Adapted from Nishizaka MK, Zaman MA, Calhoun DA. Efficacy of low-dose spironolactone in subjects with resistant hypertension. *Am J Hypertens.* 2003;16(11 Pt 1):925–930 and Chapman N, Dobson J, Wilson S, et al. Effect of spironolactone on blood pressure in subjects with resistant hypertension. *Hypertension*. 2007;49(4):839–845.

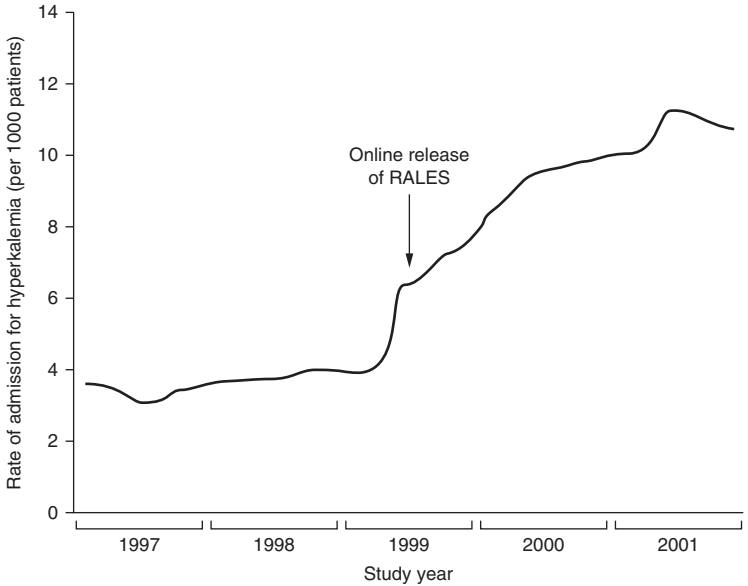


Figure 4.5. Rates of hyperkalemia after publication of the randomized aldactone evaluation study (RALES) in Ontario, Canada.

Source: Adapted from Juurlink DN, Mamdani MM, Lee DS, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *N Engl J Med.* 2004;351(6):543–551.

and over 70 additional hospital deaths per year (**Figure 4.5**).[90] In patients with CKD, this risk becomes even more profound, as reduced GFR on its own raises the risk for hyperkalemia. A recent study from 2 academic centers followed 46 patients with resistant hypertension and stages 2 or 3 CKD (mean eGFR 56.5 ± 16.2 ml/min/1.73 m^2) prescribed aldosterone blockade in addition to preexisting antihypertensive regimens, including a RAAS blocking drug and a diuretic. The investigators found that patients with a baseline eGFR $\leq$ 45 ml/min/1.73 m^2 and a serum potassium $>$4.5 mEq/l were at highest risk for hyperkalemia, defined as persistent elevation of potassium $>$5.5 mEq/l or any single reading $\geq$ 6 mEq/l.[91] This study, coupled with the relatively low rates of hyperkalemia (approximately 10%)[87] seen in clinical trials of spironolactone and eplerenone in CKD patients, suggests that very close monitoring of serum potassium should allow for safe and effective dosing of aldosterone blockade in early stage CKD patients as well as in later stage CKD patients with low baseline potassium levels.

OBESITY

In Chapter 6, we will discuss weight loss as a therapeutic intervention to mitigate or halt the effects of obesity on blood pressure and kidney function. As a complement to weight loss, or for those unsuccessful at weight loss, aldosterone blockade can serve as another therapeutic option for obese patients with resistant hypertension and/or kidney disease. Obesity and the metabolic syndrome are frequently associated with elevated levels of aldosterone,[92–97] and intentional weight loss typically reduces aldosterone levels.[98,99] Adipocytes express a renin-angiotensin system and are consequently able to produce angiotensin II, traditionally the key stimulator of adrenal production of aldosterone.[100,101] This fat-based renin-angiotensin system, however, is likely only one component of aldosterone overproduction in obesity. Excess adipose tissue appears to provide a medium in which aldosterone secretion is further stimulated by angiotensin II-independent routes.

Obesity is characterized by increased plasma fatty acids and oxidative stress; the most readily oxidized fatty acids are the polyunsaturated acids, the most abundant of which is linoleic acid. Goodfriend and colleagues tested the effects of oxidized derivatives of linoleic acid on rat adrenal cells. One derivative, 12,13-epoxy-9-keto-10(*trans*)-octadecenoic acid, was particularly potent, stimulating aldosteronogenesis at concentrations from 0.5 to 5 μmol/L.[102] This experiment suggests that, in the obese state, oxidized fatty acids likely stimulate aldosteronogenesis independent of physiologic control by angiotensin II and volume status.

Ehrhart-Bornstein and colleagues created a fat-cell conditioned medium to test the hypothesis that adipocyte secretory products directly stimulate adrenocortical aldosterone secretion. In vitro, human adrenocortical cells were placed in this fat-cell conditioned medium and, in a 24-hour incubation period, increased aldosterone secretion sevenfold. Concomitant incubation with the angiotensin receptor blocker, valsartan, did not significantly reduce this aldosterone secretion, confirming that the aldosterone-stimulating effect was not angiotensin II-mediated. At least 2 mineralocorticoid-releasing factors—an active (MW $>$ 50 kDa) and an inactive (MW $<$ 50 kDa) fraction—were identified by fractionation of the fat cell medium, but these investigators were not able to further categorize these potent, adipocyte-secreted aldosterone-stimulating factors.[103]

Complement-C1q TNF-related protein 1 (CTRP1), a member of the CTRP superfamily, may turn out be one of these mineralocorticoid-releasing factors. In an experiment with obese, diabetic rats, Jeon and colleagues recently investigated stimulation of aldosterone production by CTRP1, which is expressed at high levels in adipose tissue *and* in the zona glomerulosa of the adrenal cortex, the site of aldosterone production. In addition to finding a dose-dependent increase in aldosterone production by CTRP1, they also found that angiotensin II-induced aldosterone production was, at least in part, mediated by the stimulation of CTRP1 secretion.[104]

These pathophysiologic links between visceral adiposity and aldosterone secretion suggest that obese patients may be constitutively stimulated to produce aldosterone, and obesity can thus be viewed as a state of relative hyperaldosteronism. For example, in the study by Gaddam and others of 279 resistant hypertensive patients, the mean BMI was 33.0 kg/m^2, the mean plasma aldosterone was 13.0 ng/dl, and the mean urine aldosterone was 13.0 μg/24 hours.[84] Given that these obese subjects' mean urinary sodium excretion

was 187 mEq/24 hours, these values suggest disordered aldosterone regulation, with the average patient in the study essentially meeting clinical criteria for primary aldosteronism (urine aldosterone > 12.0 μg/24 hours with urine sodium > 200 mEq/24 hours).[105]

The role of aldosterone in obesity-related hypertension is crucial when considering pharmacologic treatment options. While ACE inhibitors and ARBs may be reasonable first-choice therapies for obese hypertensive patients, aldosterone blockade may be a more effective initial therapy. In a small study from Poland, 21 obese subjects with mean BMI 32.4 ± 3.4 kg/m^2 and 12.0 ± 7.0 years of antihypertensive therapy, including longstanding use of ACE inhibitors, were given a low dose of spironolactone (12.5 mg per day). All subjects had preexisting target organ damage from resistant hypertension—grade II or higher hypertensive angiopathy in a documented fundoscopic examination, and left ventricular hypertrophy on transthoracic echocardiography. The mean aldosterone level before spironolactone treatment was 10.1 ± 7.3 ng/dl, and over 40% of subjects had baseline levels greater than mean population levels. During 4 weeks of low-dose spironolactone, mean office, 24-hour ambulatory, and nocturnal blood pressures all declined significantly (P 0.004, P 0.03, and P 0.004, respectively, compared with baseline) (**Figure 4.6**).[106]

Similarly, aldosterone blockade could emerge as a top priority in treating obesity-associated kidney disease. Presently, the bulk of the data supporting this therapeutic strategy comes from animal studies. ACE inhibitors have been shown to ameliorate podocyte damage in obese rats, perhaps through downstream suppression of aldosterone.[107] Mineralocorticoid receptor blockers, such as spironolactone and eplerenone, which target both the epithelial and nonepithelial effects of aldosterone, have shown very promising results in animal studies of obesity-associated kidney disease. In dogs fed a high-fat diet, simultaneous treatment with eplerenone (compared with untreated animals) markedly attenuated obesity-induced glomerular hyperfiltration, sodium retention, and hypertension.[108] Proteinuria in a rat model of metabolic syndrome was correlated with aldosterone levels and accompanied histologically by podocyte injury that, along with proteinuria, markedly improved after administration of mineralocorticoid receptor blockade.[109–111]

Recently, though, some human data has emerged, highlighting the efficacy of aldosterone blockade in obesity-associated kidney disease. The aforementioned Polish study of 21 obese hypertensive patients found that mineralocorticoid receptor blockade, in addition to lowering blood pressure, also significantly reduced urinary protein excretion.[106] A 3-phase crossover study by Morales and colleagues treated 12 obese patients with proteinuric CKD (mean baseline BMI 33.8 kg/m^2, estimated GFR 57.9 ml/min/1.73 m^2, and proteinuria 2.2 g/24 hours) for 6 weeks with lisinopril 20 mg/day, lisinopril 10 mg/day + candesartan 16 mg/day, and eplerenone 25 mg/day in random order with washout periods between treatment phases. Despite a relatively short treatment course and low dose of aldosterone blockade, the proteinuria reductions seen with eplerenone treatment were superior to lisinopril therapy and equivalent to the combination therapy of lisinopril and candesartan (**Table 4.6**).[112] Notably, the mean pretreatment aldosterone levels of subjects in both of these studies were well above mean population aldosterone values,[81] supporting the notion that obesity is a hyperaldosterone state and highlighting why direct aldosterone blockade may have been so effective in these patients.

Obesity is also linked to hypertension—both essential and resistant hypertension—and kidney disease via obstructive sleep apnea (OSA), a frequent comorbidity. While sleep apnea

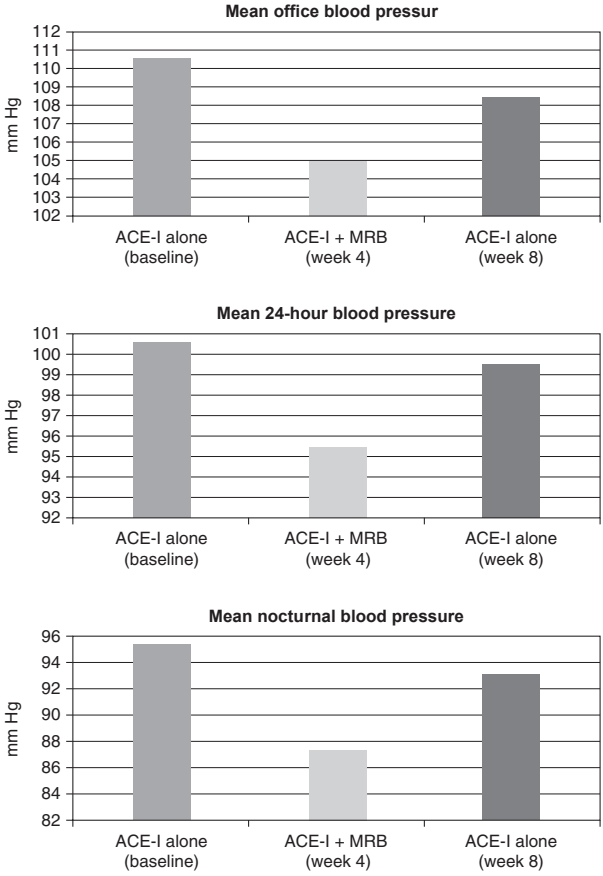


Figure 4.6. In a pre-post study of 21 obese subjects with resistant hypertension, addition of a low dose of the mineralocorticoid receptor blocker (MRB), spironolactone, to long-standing ACE-inhibitor therapy reduced office, 24-hour, and nocturnal blood pressure. These improvements in blood pressures were eradicated upon withdrawal of the MRB.

Source: Data from Bomback AS, Muskala P, Bald E, Chwatko G, Nowicki M. Low dose spironolactone, added to long-term ACE-inhibitor therapy, reduces blood pressure and urinary albumin excretion in obese patients with hypertensive target organ damage. *Clin Nephrol*. 2009;72(6):449–456.

Table 4.6. Antiproteinuric therapies in obesity

	Lisinopril 20 mg/day	Lisinopril 10 mg/day + candesartan 16 mg/day	Eplerenone 25 mg/day
Baseline proteinuria (g/24 hours, mean, range)	2.5 (0.5−8.8)	2.8 (0.5−8.2)	2.7 (0.5−9.2)
6-week reduction in proteinuria (%, mean, SD)	11.3 ± 34.8	26.9 ± 30.6	28.4 ± 31.6
>25% reduction in proteinuria by 6 weeks (n, %)	3/12 (25%)	8/12 (66.7%)	8/12 (66.7%)

Source: Data from Morales E, Huerta A, Gutierrez E, Gutierrez Solis E, Segura J, Praga M. The antiproteinuric effect of the blockage of the renin-angiotensin-aldosterone system (RAAS) in obese patients. Which treatment option is the most effective? *Nefrologia*. 2009;29(5):421–429.

can occur in nonobese individuals (e.g., patients with craniofacial or upper airway soft tissue abnormalities), obesity is the best documented risk factor for OSA, and the prevalence of OSA rises in parallel to body mass index and associated markers of obesity, such as neck circumference and waist-to-hip ratio. Sleep apnea is characterized by a repetitive partial (hypopnea) or complete (apnea) closing of the pharynx during sleep; while apneas or hypopneas that last a minimum of 10 seconds are considered clinically significant, they usually last from 20 to 30 seconds and can last more than 1 minute. OSA, defined as an average of at least 10 apneic and hypopneic episodes per sleep hour, is a common but frequently undiagnosed disorder present in about 10% of middle-aged individuals (5% of women, 15% of men).[113,114] Daytime sleepiness or fatigue is a common presenting complaint, as is the presence of snoring. The gold standard for an accurate diagnosis of OSA is a polysomnography evaluation performed in a sleep disorders unit.

Hypertension is often, by itself, an indicator of the presence of OSA: about one half of patients with hypertension have OSA, and about one half of all patients with OSA have hypertension.[115–118] A number of large studies have identified OSA as an independent risk factor for hypertension; these same studies have demonstrated that, in general, the more severe the OSA, the more prevalent and severe the hypertension.[119–122]

Frequent apneic and/or hypopneic episodes can end with arousals with spikes in blood pressure lasting several seconds and increasing the risk for nondipping hypertension,[123] a strong predictor of cardiovascular risk. Indeed, nearly 90% of patients with nondipping hypertension patterns have been found to have OSA.

Therefore, all patients with hypertension should, in the minimum, be questioned about OSA type symptoms and, if a positive history is obtained, be evaluated by sleep study. This is particularly important in obese patients with hypertension. Successful treatment of OSA usually bears a significant reduction in blood pressure levels, although in most cases the result is a reduction, rather than a complete elimination, of the need for antihypertensive medications. Treatment of OSA includes nonsurgical and surgical approaches. Weight loss and position therapy (avoiding the supine position) can reduce the frequency of apneic episodes, but nasal continuous positive airway pressure (nCPAP) remains the most effective nonsurgical form of

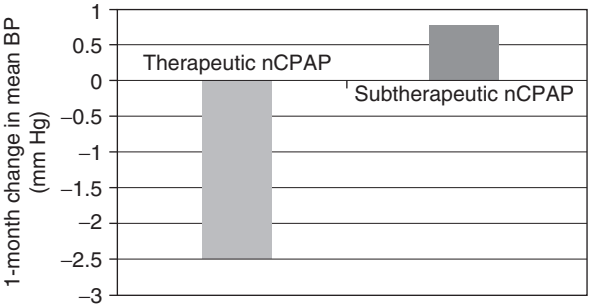


Figure 4.7. In 118 men with obstructive sleep apnea randomized to either therapeutic (n = 59) or intentionally subtherapeutic (n = 59) nasal CPAP (nCPAP) for 1 month, therapeutic nCPAP reduced mean arterial ambulatory blood pressure by 2.5 mm Hg, whereas subtherapeutic nCPAP increased blood pressure by 0.8 mm Hg (p = 0.001).

Source: Data from Pepperell JC, Ramdassingh-Dow S, Crosthwaite N, et al. Ambulatory blood pressure after therapeutic and subtherapeutic nasal continuous positive airway pressure for obstructive sleep apnoea: A randomised parallel trial. *Lancet*. 2002;359(9302):204–210.

therapy (**Figure 4.7**).[124] A wide variety of surgical procedures, including uvulopalatopharyngoplasty, relief of nasal obstruction, tonsillectomy, adenoidectomy, and somnoplasty (radiofrequency-mediated shrinkage of the tongue and soft palate), have also been used to varying degrees of success.[125]

OTHER CAUSES

Rarer causes of secondary and resistant hypertension, listed earlier in Table 4.1, should be considered in select patients. The prevalence rates of these disorders is less than 0.5%.[2] Pheochromocytomas—neuroendocrine tumors of the adrenal glands—may not always present with all of the classic symptoms of palpitations, headaches, diaphoresis, and paroxysms of hypertension. Testing for free plasma metanephrine levels has become the most efficient screening method; this can be followed by more involved 24-hour urine tests for abnormal urinary catecholamine (norepinephrine, vanillylmandelic acid) excretion and, if indicated, imaging studies with CT or MRI. Definitive therapy is surgical removal of the tumor, but alpha- and beta-adrenergic blocking drugs have also been used in conjunction with or in lieu of surgery.

Cushing's syndrome, or hypercortisolism, can be due to adrenocorticotrophic hormone-producing pituitary tumors (Cushing's disease), nonpituitary tumors that produce either adrenocorticotrophic hormone or cortisol, or chronic use of exogenous glucocorticoids. Cushingoid patients will present with obesity, striae, and edema, and their history will often

include complaints of muscle weakness. In cases of medication-induced Cushing's syndrome, the diagnosis is usually made by history and physical exam alone, and treatment involves withdrawal of the glucocorticoid agent. A full diagnostic work-up involves 24-hour urine collection for increased levels of urinary cortisol and a dexamethasone suppression test assaying plasma cortisol levels before and after the administration of 1 mg of dexamethasone. If CT or MRI imaging identifies a tumor site, surgical intervention is definitive therapy.

Coarctation of the aorta more commonly presents in childhood than adulthood, and should be considered in hypertensive patients with brachial or femoral pulse differentials as well as differential arm blood pressures. Systolic bruits in the back and/or chest may also be auscultated. Echocardiography followed by CT angiogram has traditionally been the diagnostic route, but MR imaging of the heart and aorta may emerge as the initial imaging modality in some centers. Depending on the degree of coarctation, treatment is either surgery or balloon angioplasty.

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Chapter 5

Hypertension in End Stage Renal Disease

Cardiovascular disease is the leading cause of death among hemodialysis patients. Poorly controlled blood pressure, a major risk factor for cardiovascular events, also remains one of the two most common causes of chronic kidney disease (CKD) and contributes to development of end stage renal disease (ESRD). Hypertension is a common finding in dialysis patients. At least half of hemodialysis patients—up to 85% in some series—and almost 30% of peritoneal dialysis patients are hypertensive.[1–3] As discussed in the previous chapter, the kidney plays a crucial role in the genesis of hypertension as well as the response to antihypertensive treatment. Consequently, just as the evaluation and treatment of hypertension in patients with CKD differs from the approach in individuals with normal kidney function, the therapeutic approach to hypertension in patients with ESRD should be considered as a distinct entity.

PATHOGENESIS

The pathogenesis of hypertension in ESRD is multifactorial and encompasses many of the same risk factors at play in CKD, including sodium and volume retention, hyperactivity of the renin angiotensin aldosterone system (RAAS), increased sympathetic activity, secondary hyperparathyroidism with subsequent intracellular calcium abnormalities, and heavy calcification of the peripheral vasculature. Volume expansion, however, emerges as the major factor in the development of hypertension in patients on chronic dialysis. Expanded extracellular volume increases blood pressure by raising cardiac output (via increases in stroke volume) and systemic vascular resistance.

Endothelial dysfunction also contributes to blood pressure elevations in ESRD patients. In response to mechanical and chemical stimuli, endothelial cells respond by production of hemodynamically active compounds, including the endothelial derived relaxing factor, nitric oxide, and the vasoconstrictive factor, endothelin-1. Chronic dialysis patients with overt hypertension have demonstrated abnormal endothelial release of these substance—specifically, overactivity of the vasoconstrictor, endothelin-1,[4] and undersecretion of the vasodilator, nitric oxide.[5] Clinical trials are currently exploring whether endothelin-receptor antagonists can emerge as a new class of agents for controlling hypertension.[6,7]

Calcification of the cardiovascular system is highly prevalent in ESRD patients on peritoneal dialysis and hemodialysis and can persist following successful kidney transplantation. This progressive vascular calcification is associated with arterial stiffness, hypertension, and increased cardiovascular mortality.[8–11] Hypertension, dyslipidemia, glucose intolerance, and high serum homocysteine levels contribute to calcification in both CKD and ESRD patients, but the role of abnormal calcium-phosphorus metabolism takes on particular importance in late and end stage kidney disease.[12] A striking example of this phenomenon comes from the study by Goodman and colleagues, in which electron beam CT scans were used to screen for coronary artery calcification in 39 young hemodialysis patients (age range 7–30 years of age) and in 60 control subjects between the ages of 20 and 30 years.[13] Calcification was present in 14 of the 16 dialysis patients (88%) who were 20–30 years old, but only in 3 of the 60 control subjects (5%). Duration of dialysis, mean serum phosphorus concentration, mean calcium–phosphorus ion product in serum, and the daily intake of calcium were all significantly higher among the dialysis patients with coronary-artery calcification. In 10 patients with calcification

who underwent follow-up CT scanning, the calcification score nearly doubled over a mean period of 20 months.

BLOOD PRESSURE TARGETS

To date, there have been no prospective, randomized trials evaluating target blood pressure in dialysis patients with hard outcomes such as myocardial infarction, stroke, and mortality. Current blood pressure targets for the ESRD population, therefore, have been extrapolated from the 130/80 mm Hg target for patients with CKD. Blood pressures tend to fluctuate during and after dialysis sessions, though, prompting most nephrologists to individualize their blood pressure targets for their dialysis patients and often set different predialysis and postdialysis blood pressure goals—for example, below 140/90 mm Hg predialysis and below 130/80 postdialysis.[14,15]

The J-curve phenomenon, discussed in Chapter 2, may hold particularly true in the dialysis population. A number of observation and retrospective studies have suggested that extremely low systolic blood pressures are associated with increased risk for mortality. The largest observational study grouped 56,338 incident and 69,590 prevalent hemodialysis patients into the following 6 predialysis systolic blood pressure categories: (1) <120 mm Hg, (2) between 120 and 140 mm Hg, (3) between 140 and 160 mm Hg, (4) between 160 and 180 mm Hg, (5) between 180 and 200 mm Hg, and (6) >200 mm Hg. The 1-year mortality hazard ratios for patients in categories 1 and 2 (i.e., predialysis systolic blood pressure <140 mm Hg) were 2.63 to 3.68 and 1.57 to 1.68 compared with category 4, the reference group, whereas hazard ratios for categories 3, 5, and 6 were not different from category 4. Time-varying models magnified category 1 and 2 hazard ratios to 5.54–7.42 and 1.92–2.21, such that 25–35% of patients in the target SBP range (<140 mm Hg) had the greatest risk for death.[16] The J-curve phenomenon has also been demonstrated in peritoneal dialysis patients, who tend to run, on average, lower blood pressures than hemodialysis patients. An analysis of over 1000 peritoneal dialysis patients, using 111–120 mm Hg systolic blood pressure as the reference group, found that systolic blood pressures below 110 mm Hg more than doubled mortality risk (**Figure 5.1**).[17]

In contrast to these findings, however, stands the recent meta-analysis by Heerspink and colleagues, in which antihypertensive treatment, regardless of baseline blood pressure, emerged as an independent, risk-reducing intervention for dialysis patients.[18] These authors pooled data from 8 randomized, controlled trials of blood pressure lowering in patients on dialysis that reported cardiovascular outcomes. These trials provided data for 1679 patients and 495 cardiovascular events. Weighted mean systolic blood pressure was 4.5 mm Hg lower and diastolic blood pressure 2.3 mm Hg lower in actively treated patients than in control subjects. Overall, blood pressure lowering treatment was associated with lower risks of cardiovascular events (RR 0.71, 95% CI 0.55–0.92), all-cause mortality (RR 0.80, CI 0.66–0.96), and cardiovascular mortality (RR 0.71, CI 0.50–0.99) than control regimens. Therefore, while untreated lower blood pressures may be a marker of increased morbidity and morality, treated low blood pressures likely do not imply the same risk.

Given the daily, volume-associated fluctuations of blood pressure in dialysis patients, the proper time and method to measure blood pressure is vitally important. Use of 24-hour

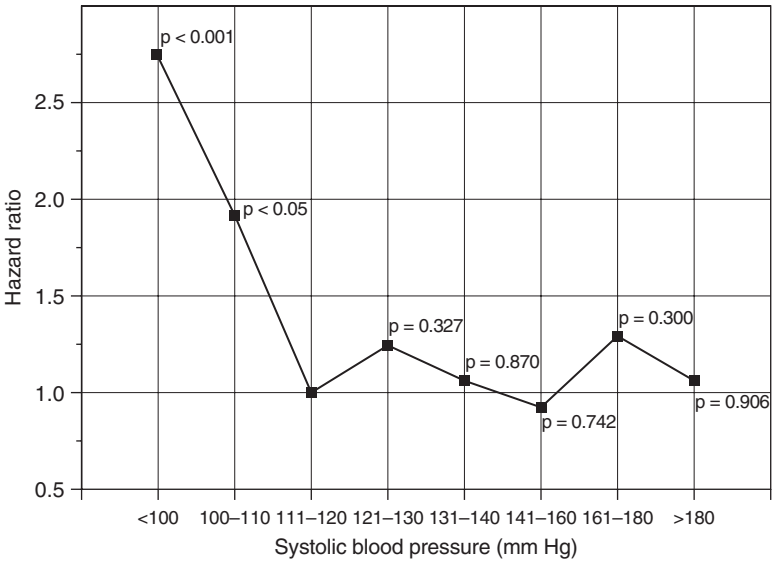

Figure 5.1. The association of systolic blood pressure categories with all-cause mortality in 1053 peritoneal dialysis patients. Mortality risk was evaluated in a proportional hazard model using the 111–120 mm Hg group as a reference group.

Source: Reprinted with permission from Goldfarb-Rumyantzev AS, Baird BC, Leypoldt JK, Cheung AK. The association between BP and mortality in patients on chronic peritoneal dialysis. *Nephrol Dial Transplant*. 2005;20(8): 1693–1701 with permission from Oxford University Press.

ambulatory blood pressure monitoring (ABPM), as previously discussed, is a useful tool to assess whether blood pressure is being adequately managed.[19] A great deal of work from Agarwal and colleagues has culminated in some general observations about blood pressure management in CKD and dialysis patients,[20,21] including the importance of nocturnal blood pressure as a variable for cardiovascular risk and the measurement of blood pressure by home monitoring on postdialysis days as a better reflection of true pressure level. While these observations need confirmation, they currently provide a framework by which to assess proper antihypertensive management.

DRY WEIGHT

Excess volume is considered the most important factor causing hypertension in patients on hemodialysis.[22] Indeed, ESRD patients on peritoneal dialysis, a daily treatment modality that allows for more efficient control of volume than thrice-weekly hemodialysis, generally run

much lower blood pressure values than patients on hemodialysis. In observational studies, volume reduction via salt-restricted diets and increased ultrafiltration volumes has been associated with blood pressure improvements in up to 90% of hemodialysis patients.[23–25] Reports from dialysis centers in Europe have demonstrated that control of volume expansion by means of long-duration hemodialysis can result in remarkable hypertension control and frequently obviate the need for antihypertensive medication.[26–28]

The term *dry weight*, or *target weight*, is defined colloquially as the weight a patient should have after dialysis, and more scientifically as "the post-hemodialysis weight at which the patient is as close as possible to a normal hydration state without experiencing symptoms indicative of over or underhydration at or after the end of hemodialysis treatment."[29, p. 543] In hemodialysis centers, the dry weight is usually prescribed in a trial-and-error fashion, with blood pressure being the main clinical parameter used to monitor success or failure; patients experiencing low postdialysis blood pressures often have their dry weights raised, while very hypertensive patients conversely have their dry weights lowered. Again stressing the crucial role of volume control in treating hypertension, the optimal dry weight for a hemodialysis patient can be viewed as the postdialysis weight at which blood pressure remains controlled without antihypertensive medication.[27]

The Dry-Weight Reduction in Hypertensive Hemodialysis Patients (DRIP) trial, recently reported, was the first randomized, controlled trial designed to determine whether additional volume reduction will result in blood pressure improvement among hypertensive dialysis patients. One hundred fifty long-term hemodialysis patients were randomized to ultrafiltration ($n = 100$) or control ($n = 50$) groups. In the ultrafiltration group, an additional weight loss of 0.1 kg/10-kg body weight was prescribed per dialysis without increasing dialysis time or frequency (a protocol to reduce this additional ultrafiltration was used if patients developed signs or symptoms such as muscle cramps, need for excessive saline, or symptomatic hypotension). The 50 control patients did not have any reduction in their standard dry weight. The primary outcome was change in interdialytic systolic ambulatory blood pressure. At 4 weeks, a postdialysis decrease in weight of 0.9 kg in the ultrafiltration group resulted in a systolic and diastolic blood pressure reduction of 6.9/3.1 mm Hg. At 8 weeks, a similar reduction in BP occurred with a 1-kg reduction in dry weight (**Figure 5.2**).[30]

Almost 2 decades ago, hypertension control without medication was shown to be the best single marker of survival in hemodialysis patients.[31] Volume excess, therefore, is well recognized as a major contributor to the high rates of cardiovascular morbidity and mortality in ESRD, yet it has been difficult to achieve euhydration in ESRD patients given the somewhat subjective nature of dry weight assessments. Even if blood pressure, rather than weight itself, is used as a surrogate marker of hydration, too often patients begin dialysis sessions with inappropriately high blood pressures or terminate dialysis sessions with equally inappropriate low pressures. Overall, clinical judgment has been relatively insensitive in detecting subtle to significant volume expansion, highlighting the need for more reliable, quantitative techniques that can be used at the bedside to augment the clinical examination. In recent years, objective methods for assessing dry weight have been studied, including cardiothoracic ratio on X-ray, electron beam CT scan of lung density, vena cava diameter and collapsibility, and serum levels of natriuretic peptides.[32]

Bioelectric impedance analysis (bioimpedance) is a noninvasive means of measuring body composition that has been used in research studies of CKD and ESRD patients on dialysis.[33–38] This bedside technique, available since the 1980s, measures the electric impedance, or opposition

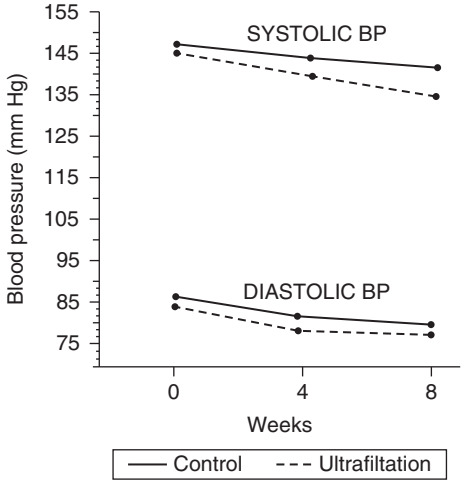

Figure 5.2. The effect of dry-weight reduction on interdialytic ambulatory systolic and diastolic blood pressure in hypertensive hemodialysis patients in the DRIP trial.

Adapted from Agarwal R, Alborzi P, Satyan S, Light RP. Dry-weight reduction in hypertensive hemodialysis patients (DRIP): a randomized, controlled trial. *Hypertension*. 2009;53(3):500–507.

to the flow of electric current in body tissues, which can then be used to calculate an estimate of total body water (TBW), extracellular volume (ECV), and intracellular volume. Bioimpedance provides an opportunity to detect occult (i.e., not clinically apparent) volume expansion in patients with kidney impairment, and therefore bioimpedance measurements before, during, and after dialysis could, in theory, be used to achieve phsyiologic dry weight and a state of euhydration that matches volume measurements in individuals with normal kidney function.[33,35,39,40]

In bioimpedance studies of dialysis patients, pretreatment measurements show a state of hyperhydration in which ECV is 45–55% of TBW depending on the degree of interdialytic weight gain; in healthy control subjects, in contrast, ECV is typically 35–45% TBW depending on the amount of dietary salt intake (**Table 5.1**).[41] In a recent study using bioelectric impedance analysis to measure the hydration status of 269 prevalent hemodialysis patients, overhydration (ECV 51% of TBW) was associated with longer dialysis vintage, higher predialysis and postdialysis blood pressures, greater use of antihypertensive medications, and increased mortality rates compared to normohydration (ECV 48% of TBW) (**Table 5.2**); in multivariate analysis, overhydration was an independent predictor of mortality.[38] It is conceivable that, in the future, target dialysis weights will be based on bioimpedance recordings, with patients

Table 5.1. Whole-body bioimpedance measurements of (A) healthy volunteers on low-, normal-, and high-salt diets, and (B) hemodialysis subjects at varying degrees of interdialytic weight gain

(A) Healthy Volunteers

Volunteer 1		Volunteer 2		Volunteer 3		Volunteer 4		Volunteer 5	
Dietary Salt Intake	ECV (% TBW)	Dietary Salt Intake	ECV (%TBW)	Dietary Salt intake	ECV (% TBW)	Dietary Salt Intake	ECV (% TBW)	Dietary Salt Intake	ECV (% TBW)
Low	42.3	Low	39.9	Low	42.1	Low	32.6	Low	39.9
Normal	42.8	Normal	41.1	Normal	44.9	Normal	35.1	Normal	40.9
High	46.8	High	41.4	High	45.0	High	39.5	High	41.0

(B) Hemodialysis Subjects

Subject 1		Subject 2		Subject 3		Subject 4		Subject 5	
Kg Above EDW	ECV (% TBW)	Kg Above EDW	ECV (% TBW)	Kg Above EDW	ECV (% TBW)	Kg Above EDW	ECV (% TBW)	Kg Above EDW	ECV (% TBW)
4.0	42.6	3.4	51.9	4.1	46.8	1.2	52.8	2.7	43.1
3.3	54.5	3.1	51.8	3.2	49.6	1.1	51.8	2.2	44.6
2.5	45.6	3.0	51.4	2.5	43.9	0.7	50.3	2.0	41.7

ECV, extracellular volume; TBW, total body water; EDW, estimated dry weight.

Source: Data from Bomback AS, Kshirsagar AV, Ferris ME, Klemmer PJ. Disordered aldosterone-volume relationship in end stage kidney disease. *J Renin Angiotensin Aldosterone Syst*. 2009;10(4):230–236.

Table 5.2. Mean characteristics of hyperhydrated and normohydrated hemodialysis patients in a bioimpedance study assessing the mortality risk of volume excess

	Hyperhydrated	Normohydrated
Number of patients	58	211
Age	65 years	66 years
Weight	66.6 kg	72.9 kg
Dialysis vintage	57.3 months	37.6 months
Intradialytic weight loss	3.7%	3.1%
Ultrafiltration volume	2.28 L	2.25 L
Pre-HD blood pressure	142/77 mm Hg	135/74 mm Hg
Post-HD blood pressure	143/78 mm Hg	128/74 mm Hg
Number of antihypertensive medications	1.5	1.0
BIA measurements		
Extracellular volume (L)	17.6 L	16.1 L
Total body water (L)	34.5 L	33.3 L
ECV/TBW (%)	51.0%	48.3%
Mortality in 3.5 years	41%	30%

HD, hemodialysis; BIA, bioelectrical impedance analysis; ECV, extracellular volume; TBW, total body water.

Source: Data from Wizemann V, Wabel P, Chamney P, et al. The mortality risk of overhydration in haemodialysis patients. *Nephrol Dial Transplant.* 2009;24(5):1574–1579.

being dialyzed down to an ECV—rather than weight or ultrafiltration volume—measurement that is deemed euhydration.[39,42]

NOCTURNAL AND DAILY HEMODIALYSIS

Given the crucial role of volume status in blood pressure control and overall morbidity and morality in the dialysis population, there has been a push toward more frequent and longer dialysis to achieve better volume control and, consequently, improved outcomes.[43] The randomized, controlled HEMO trial of 1846 patients undergoing thrice-weekly hemodialysis found that a higher dose of dialysis did not improve outcomes over standard, lower doses of dialysis.[44] The results from this trial have been used to argue against more frequent dialysis prescriptions, yet it is important to note that HEMO participants were randomized to low- or high-flux dialyzer membranes and standard or high Kt/V_{urea} doses, not to longer times or different ultrafiltration volumes and rates. An equally informative study is the Dialysis Outcomes

Table 5.3. Cardiovascular parameters that can be positively affected by changing patients from conventional hemodialysis to alternative dialysis modalities employing increased time and/or frequency

Short, Daily Hemodialysis	Long, Nocturnal, Daily Hemodialysis
Hypertension	Hypertension
Left ventricular hypertrophy	Left ventricular hypertrophy
Sympathetic activity	Heart failure
	Vascular reactivity/endothelial function
	Sleep hypoxemia

Source: Adapted from Chazot C, Jean G. The advantages and challenges of increasing the duration and frequency of maintenance dialysis sessions. *Nat Clin Pract Nephrol.* 2009;5(1):34–44.

and Practice Patterns study, done in 2 phases from 1996 to 2004, in which mortality was significantly increased in hemodialysis patients with an ultrafiltration rate over 10 ml/kg per hour.[45] As longer or more frequent dialysis allows for lower ultrafiltration rates with equal and often greater total volume removal, the Dialysis Outcomes and Practice Patterns study results argue that alternative dialysis strategies could prove beneficial for dialysis patients.

Short daily hemodialysis and long nocturnal daily hemodialysis have emerged as the two leading alternative dialysis strategies to conventional, thrice-weekly hemodialysis. Both of these modalities have been shown to improve blood pressure control in patients switched from conventional hemodialysis.[46–48] In addition, these more frequent routes of dialysis have demonstrated favorable effects on other cardiovascular markers such as left ventricular hypertrophy, ejection fraction, peripheral resistance, and sleep hypoxemia (**Table 5.3**).[49–53]

Presumably, these effects are mediated through improved, more efficient handling of extracellular volume. An ESRD patient on a typical Western diet, including sodium intake $\geq$150 mEq/day, may gain 3–4 kg through extracellular volume expansion every 2–3 days between thrice-weekly hemodialysis sessions. Blood pressure tends to parallel these weight gains due to saline retention, but vigorous ultrafiltration may result in intradialytic hypotension because of the lag time in plasma volume refilling from the interstitial compartment.[54] Thus, thrice-weekly dialysis may not afford enough time to safely remove the retained volume.

In addition to improved volume control, daily or nocturnal hemodialysis has been shown, in some studies, to improve the anemia and bone-mineral metabolism complications of ESRD.[55] As discussed earlier, these complications have been linked to elevated blood pressure in the dialysis population via exposure to erythropoiesis-stimulating agents and increased calcification of the vasculature. In addition, longer or more frequent dialysis might enhance the clearance of or reduce the exposure to toxins that injure the endothelium.

Thus, these alternative dialysis modalities present a number of routes by which blood pressure in dialysis patients can be improved, which in turn should translate to reduced morbidity and mortality. In fact, observational data thus far have shown positive effects of increased dialysis frequency and longer dialysis time on overall patient survival. Kjellstrand and colleagues reported a 5-year survival of 65% and a 9-year survival of 50% on 415 daily hemodialysis

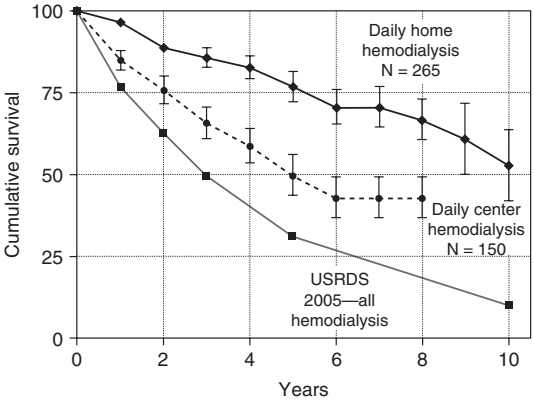

Figure 5.3. Survival curves comparing daily hemodialysis (home and in-center) versus conventional, thrice-weekly hemodialysis.

Reprinted with permission from Kjellstrand CM, Buoncristiani U, Ting G, et al. Short daily haemodialysis: survival in 415 patients treated for 1006 patient-years. *Nephrol Dial Transplant.* 2008;23(10):3283–3289 with permission from Oxford University Press.

patients from the United States, France, Italy, and the United Kingdom. Compared to United States Renal Data System (USRDS) survival data, the 5-year mortality of home and in-center daily hemodialysis patients was, respectively, one third and two thirds that of patients on conventional, thrice-weekly hemodialysis (**Figure 5.3**).[56] The Frequent Hemodialysis Network Trials Group is conducting 2 multicenter, randomized trials comparing conventional, thrice-weekly hemodialysis with in-center daily and home nocturnal hemodialysis. Subjects will be followed for 1 year and followed for a number of outcomes including mortality, left ventricular mass index, blood pressure, phosphorus, use of erythropoiesis-stimulating agents, and rates of non-access hospitalization.[57]

ANTIHYPERTENSIVE MEDICATIONS

Antihypertensive drugs are needed for dialysis patients who remain hypertensive despite efforts at maintaining euhydration. In a large, Australian-based study of 1087 patients on dialysis performed more than a decade ago, 653 (60%) patients were hypertensive according to the World Health Organization (WHO) classification: 425 (39%) patients had mild or moderate hypertension (systolic blood pressure 140–179 mm Hg and/or diastolic blood pressure 90–109 mm Hg), while 228 (21%) patients had severe hypertension (systolic blood pressure ≥180 mm Hg and/or diastolic blood pressure ≥110 mm Hg). Patients with mild or moderate hypertension needed, on average, 1.5 blood pressure medications, while those with severe hypertension required 3.3 antihypertensive drugs. Calcium channel blockers

were the most frequently administered antihypertensive drugs, used in 71% of the patients, followed by ACE-inhibitors, alpha-blockers, and beta-blockers.[58]

Given the benefits of ACE inhibitors and angiotensin receptor blockers (ARBs) in patients with heart failure, a common comorbidity in the dialysis population, these drug classes are ideal choices as antihypertensive agents. In addition, these agents may help preserve residual renal function in dialysis patients, a particularly important end point in peritoneal dialysis patients. The concern with using these drugs and the reason for their underuse in the dialysis population lies in their tendency to raise serum potassium levels. ACE inhibitors and ARBs can also reduce the secretion of and/or interfere with the action of erythropoietin.[59,60] This dampening of erythropoiesis even occurs in patients receiving erythropoietin supplementation, thus potentially exacerbating the anemia of kidney failure. Still, careful monitoring of hemoglobin and potassium values should allow more widespread use of these important drugs. A parallel case can also be made for mineralocorticoid receptor blockers, which have similar benefits in reducing morbidity and mortality in heart failure and may be particularly beneficial in the dialysis population marked by abnormally high aldosterone levels (**Figure 5.4**).[41,61,62]

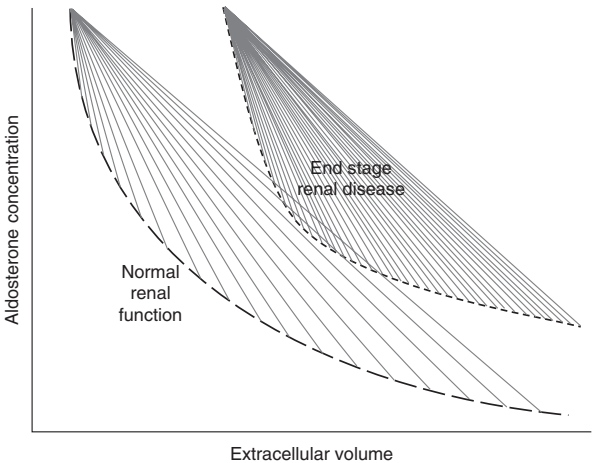

Figure 5.4. In healthy volunteers, a salt load leads to expansion of extracellular volume (ECV) and resultant suppression of aldosterone. Poor or absent renal function, manifest in hemodialysis subjects, results in higher levels of ECV; a defective volume receptor in end-stage renal disease translates to inadequate suppression of aldosterone concentrations. Thus, the aldosterone-volume curve shifts to the right in end-stage renal disease.

Adapted and based on data from Bomback AS, Kshirsagar AV, Ferris ME, Klemmer PJ. Disordered aldosterone-volume relationship in end stage kidney disease. *J Renin Angiotensin Aldosterone Syst.* 2009;10(4): 230–236.

Patients who have suffered a myocardial infarction or have heart failure due to systolic dysfunction are often prescribed beta-blockers. Given the tremendous burden of cardiovascular disease in dialysis patients, the indications for using these drugs are, not surprisingly, frequently present. When beta-blockers are used in dialysis patients, therapy should be initiated at low doses to minimize the risk of hemodynamic deterioration. In addition, the risk of bradycardia may be enhanced in the dialysis population.

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Chapter 6

Approaches to Hypertension in Chronic Kidney Disease

DIETARY AND LIFESTYLE INTERVENTIONS

Dietary and lifestyle modifications to lower blood pressure are universally recommended strategies to prevent and treat hypertension for patients with and without CKD (**Table 6.1**). Because patients with CKD often have significant comorbidities in addition to hypertension, for which lifestyle modifications are recommended, such as diabetes, obesity, and dyslipidemia, these nonpharmacologic interventions take on added importance. Controlled trials evaluating lifestyle modifications for blood pressure management in CKD are limited, however, and many of the guideline recommendations made for CKD patients are drawn from studies in patients with normal renal function.[1,2]

Dietary Salt Intake

Salt restriction has been shown to lower blood pressure in individuals with and without hypertension, and with and without kidney disease (**Figure 6.1**).[3] Patients with CKD should be considered

Table 6.1. Dietary and lifestyle modifications to manage hypertension[a]

Modification	Recommendation	Approximate SBP Reduction (range)
Weight loss	Maintain normal body weight with goal body mass index 18.5–24.9 kg/m^2	5–20 mm Hg per 10 kg weight loss
Adopt DASH-style diet[b]	Consume a diet rich in fruits, vegetables, and low-fat dairy products with a reduced content of saturated and total fat	8–14 mm Hg
Salt-restricted diet	Reduce dietary sodium intake to ≤100 mmol/day (≤2.4 g/day)	2–8 mm Hg
Physical activity	Engage in regular aerobic physical activity (e.g., brisk walking) at least 30 minutes per day, most days of the week	4–9 mm Hg
Moderation of alcohol consumption	Limit consumption to no more than 2 drinks per day (men) and 1 drink per day (women and lighter weight individuals)	2–4 mm Hg

DASH, Dietary Approaches to Stop Hypertension.

[a] The effects of these interventions are dose and time dependent and can vary for some individuals.

[b] Note that this low-sodium, high-potassium diet should be prescribed with caution in patients with CKD stage 4 or higher due to the risk of hyperkalemia.

Source: Adapted from Chobanian AV, Bakris GL, Black HR, 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):2560–2572.

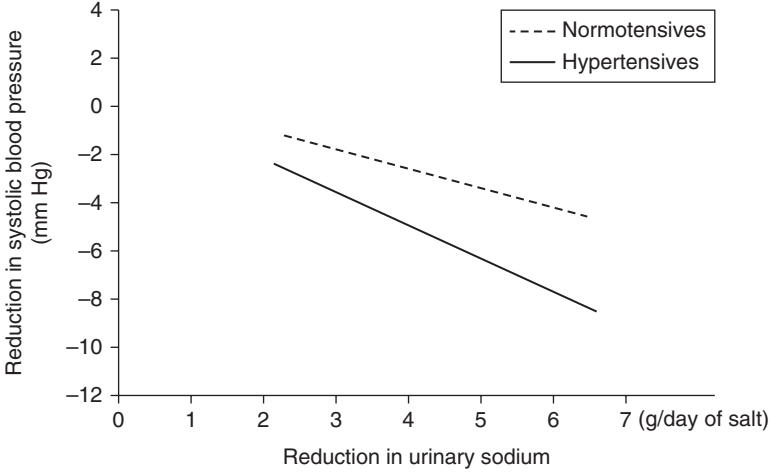


Figure 6.1. Relationship between the reduction in 24-hour urinary sodium (reflecting a reduction in dietary salt intake) and the change in blood pressure in a meta-analysis of modest salt reduction trials.

Adapted from He FJ, MacGregor GA. A comprehensive review on salt and health and current experience of worldwide salt reduction programmes. *J Hum Hypertens.* 2009;23(6):363–384.

sodium avid due to the kidney's impaired ability to effectively excrete sodium (later in this chapter, this salt avidity will be important when we discuss the use of diuretics in CKD). When the normal kidney is confronted with a sodium load, the physiologic response should be to excrete the excess sodium. When a diseased kidney with a natriuretic handicap is confronted with a sodium load, the only way to reestablish salt balance is to raise blood pressure with an ensuing pressure natriuresis.[4,5] Thus, patients with chronic kidney disease demonstrate salt-sensitive hypertension, which is defined as an abnormal increase in blood pressure in response to increased salt intake.[6] This elevation in blood pressure comes at the expense of hypertension-related cardiovascular and renal damage. Consequently, salt restriction should be beneficial for all patients with CKD, and limitation of daily sodium intake to a goal of 2 g/day (and not exceeding 4 g/day) is a logical therapeutic approach to accompany pharmacologic therapies in managing hypertension in CKD.

Salt, in addition to raising blood pressure by the mechanism just described, also may exert a direct toxic effect on the kidney (**Figure 6.2**).[7–9] High salt intake has been shown, in animal models, to generate reactive oxygen species and stimulate inflammatory cytokines. The experiments of Ying and Sanders, for example, have demonstrated a direct relationship between greater salt intake and increased renal cortical concentration of transforming growth factor-β

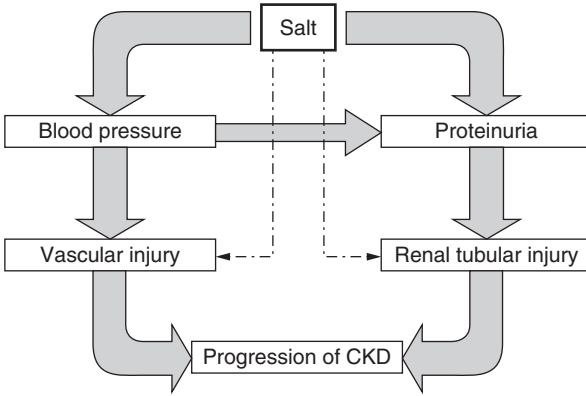


Figure 6.2. The interplay between increased dietary salt, hypertension, and proteinuria increases the risk for progression of kidney disease.

Adapted from Mishra SI, Jones-Burton C, Fink JC, Brown J, Bakris GL, Weir MR. Does dietary salt increase the risk for progression of kidney disease? *Curr Hypertens Rep*. 2005;7(5):385–391.

in rats.[10,11] Cytokines such as transforming growth factor-β, stimulated by salt excretion, can cause progressive vascular dysfunction both in the systemic circulation and within the kidney. This injury is often first expressed, clinically, by increases in proteinuria. Not surprisingly, salt restriction has an antiproteinuric effect on its own and, when combined with ACE inhibitors or angiotensin receptor blockers (ARBs), enhances the antiproteinuric benefits of RAAS blockade, even more so than diuretics (**Figure 6.3**).[12,13]

The interaction between salt and the RAAS bears mention as a key player in kidney injury in modern society. In particular, the interaction between the terminal component of the RAAS, aldosterone, and high salt intake has been linked, in both animal and human experiments, to hypertension, heart failure, and kidney disease.[14–20] The role of aldosterone in hypertension and kidney disease was already discussed in Chapter 4, and again we note that aldosterone-mediated injuries almost exclusively occur in the setting of normal to high salt intake.

To understand the importance of this sodium cofactor, it is important to know that the first RAAS-blocking drugs, ACE inhibitors, were developed using an extract of the venom of the Brazilian pit viper, *Bothrops jararaca*. Like most terrestrial animals, *Bothrops jararaca* evolved in an environment with limited salt. The natural enemies of the Brazilian pit viper evolved under similar environmental, evolutionary pressures. Among these enemies is man—in northern Brazil and southern Venezuela, the species is typified by the Yanomamo Indians, who were studied in the 1970s as one of the most primitive, culturally intact tribes in existence. This anthropologic research led to a landmark publication on the tribe's no-salt culture, which was reflected in very low blood pressures despite markedly elevated renin and aldosterone concentrations (i.e., a hyperactive RAAS).[21] The subsistence patterns of the Yanomamo dictated a reliance on

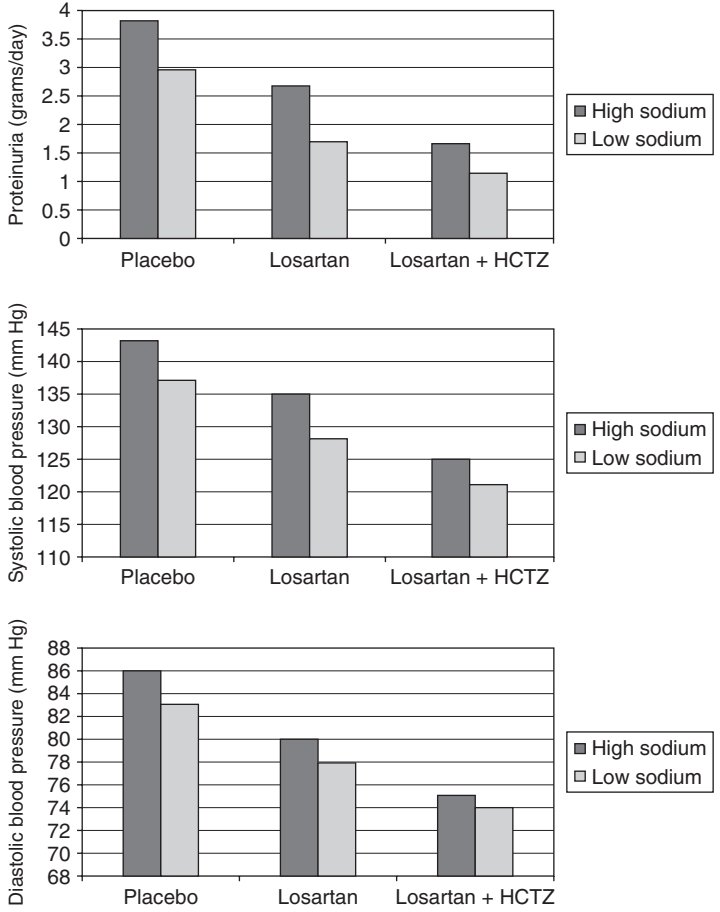


Figure 6.3. A low-salt diet reduces blood pressure and proteinuria even in the absence of anti-proteinuric drugs. The proteinuria reductions achieved with RAAS blockade (e.g. the ARB, losartan) are enhanced by salt restriction, and even further improved by combining salt restriction and a diuretic.

Adapted from Vogt L, Waanders F, Boomsma F, de Zeeuw D, Navis G. Effects of dietary sodium and hydrochlorothiazide on the antiproteinuric efficacy of losartan. *J Am Soc Nephrol.* 2008;19(5):999–1007.

RAAS-dependent normotension to ensure adequate blood flow to all organs, and ACE inhibitors, like the venom of the Brazilian pit viper, would be toxic to these individuals.[22] Therefore, in modern, relatively high-salt societies such as ours, overactivity of the RAAS is essentially a maladaptive response that has persisted from our low-salt ancestors. This maladaptive physiology of an overactive RAAS is exacerbated when a diseased kidney cannot efficiently excrete sodium, which is the case in CKD.

While nearly all patients with CKD likely exhibit some degree of salt sensitivity, the phenomenon is particularly troublesome for certain patient populations. Black patients, regardless of baseline blood pressure, exhibit more salt sensitivity than whites.[23,24] This difference of renal sodium handling was borne out by the results of the Dietary Approaches to Stop Hypertension (DASH) diet, in which hypertensive black females had a 6 mm Hg greater reduction in blood pressure compared to hypertensive white females on a low-sodium diet.[25] Hypertensive individuals of African descent, who excrete sodium less efficiently during the daytime than hypertensive individuals of European descent, have an associated increase in daytime systolic blood pressure and also an associated blunted nocturnal blood pressure dipping response.[26] A difference in kidney function has been postulated as the etiology of this increased salt sensitivity in blacks: a careful balance study comparing black and white subjects before and after furosemide administration found a more active sodium-potassium-chloride cotransporter (NKCC2) in the thick ascending limb in blacks but not whites.[27]

Obesity and the metabolic syndrome are states of impaired sodium excretion,[28] and this salt avidity is amplified when kidney dysfunction accompanies these disease states. The natriuretic handicap of obesity and the metabolic syndrome is likely caused by insulin resistance and/or hyperglycemia, as increased filtered glucose stimulates tubular reabsorption of filtered sodium.[29] An alternative theory is that the hyperfiltration of obesity—an overwork of the kidney from increased filter load—causes a concomitant hyperactivity of the proximal tubule, with subsequent excessive sodium reabsorption.[30] The impaired sodium excretion in obesity has been postulated as, potentially, the fundamental root of obesity-associated hypertension.[31,32] Not surprisingly, obese blacks are particularly at high risk for hypertension and hypertension-related target organ damage. A study of 397 African Americans, of whom roughly half were hypertensive, reported a 94% prevalence of hypertension in metabolic syndrome subjects compared to 37% in subjects without metabolic syndrome.[33]

Sugar Soda, High-Fructose Corn Syrup, and Uric Acid

Fructose consumption has been on an explosive rise, increasing nearly 2000% over the past 3 decades, and has paralleled the epidemics of obesity, metabolic syndrome, hypertension, and CKD.[34] Estimates from the US Department of Agriculture report the average yearly intake of high-fructose corn syrup as an added sugar to be as high as 62.4 pounds per person. Sugar-sweetened beverages, such as regular soft drinks and flavored fruit drinks, account for more than 70% of this intake.[35] The metabolism of fructose, unique to that of other sugars, leads to depletion of hepatic adenosine triphosphate, increasing the degradation of nucleotides and driving the synthesis of uric acid.[36] Data from the Third National Health and Nutrition Examination Survey (NHANES) suggested a link between regular, but not diet, soda consumption and the frequency of hyperuricemia,[37] a concerning finding in light of recent epidemiologic studies in which elevated uric acid levels independently increased the risk for hypertension and kidney disease.[38–42]

Experimental data support a link between fructose intake, hyperuricemia, increases in blood pressure, and subsequent kidney damage. In animals, fructose-associated hyperuricemia produces a metabolic syndrome associated with systemic and glomerular hypertension, renal hypertrophy, and arteriolopathy of the renal vasculature, with resultant reductions in creatinine clearance and increases in proteinuria.[36,43–45] Treating these animals with xanthine oxidase inhibitors (e.g., allopurinol) lowers uric acid levels and partially prevents these changes.[36,46] High-fructose diets, compared to high-glucose diets, administered to healthy volunteers have been shown to induce many features of the metabolic syndrome, including elevations in blood pressure.[47,48]

The controversy over the potential dangers of sodas and beverages sweetened with high-fructose corn syrup has been playing out not only in the medical literature[49–53] but also in the mainstream media, including advertising campaigns funded by the corn-producing industry (available at www.sweetsurprise.com). Defenders of high-fructose corn syrup point out that this sweetener is comprised of approximately 40–55% fructose (the other components being glucose and readily hydrolyzable polymers of glucose), and findings from animal and human studies that use 100% fructose formulations are not necessarily applicable to high-fructose corn syrup.[54]

Therefore, today's regular soft drinks, sweetened with high-fructose corn syrup, may not substantially differ from soft drinks of 30–40 years ago that were sweetened with sucrose, which is also comprised of 50% fructose and 50% glucose. The parallel epidemics of obesity, metabolic syndrome, hypertension, and CKD, then, would not be due to soda (and high-fructose corn syrup) consumption but instead explained by behaviors and lifestyles that tend to accompany soda consumption, such as increased total caloric intake, reduced physical activity, and higher salt diets.[55,56] Notably, a recently published, large epidemiologic study using data from the Nurses' Health Study 1 (N = 88,540), Nurses' Health Study 2 (N = 97,315), and the Health Professionals Follow-up Study (N = 37,375) found no association between fructose intake and the risk for incident hypertension over 14–20 years of follow-up.[57] While cross-sectional studies have suggested an association between increased sugar soda intake and prevalent kidney disease in the form of elevated serum creatinine[58] and microalbuminuria,[59] 2 longitudinal studies found no relationship between sugar soda consumption and either incident kidney disease[60] or progression of preexistent CKD (**Figure 6.4**).[61]

There is less controversy about elevated uric acid levels leading to elevations in blood pressure. Numerous studies have found that hyperuricemia, independent of other risk factors, increases the risk for developing hypertension within 10 years. In the Framingham Heart Study, for example, multivariate analyses (adjusting for factors such as age, sex, body mass index, smoking, alcohol intake, and renal function) revealed that a 1 standard deviation higher serum uric acid level was associated with an odds ratio of 1.17 (95% CI, 1.02 to 1.33) for developing hypertension and an odds ratio of 1.11 (95% CI, 1.01 to 1.23) for progression to a higher blood pressure stage.[38] Hyperuricemia is common among adults with prehypertension, especially when microalbuminuria is present,[62,63] and it is observed in up to 60% of patients with untreated essential hypertension.[64–66] Animal studies, cited earlier, have shown that lowering uric acid levels with xanthine oxidase inhibitors such as allopurinol can lower blood pressure and mitigate hypertensive target organ damage. Preliminary clinical data have shown similar benefit in humans. A double-blind, placebo-controlled crossover trial of allopurinol in 30 adolescents with hyperuricemia and hypertension found that allopurinol significantly

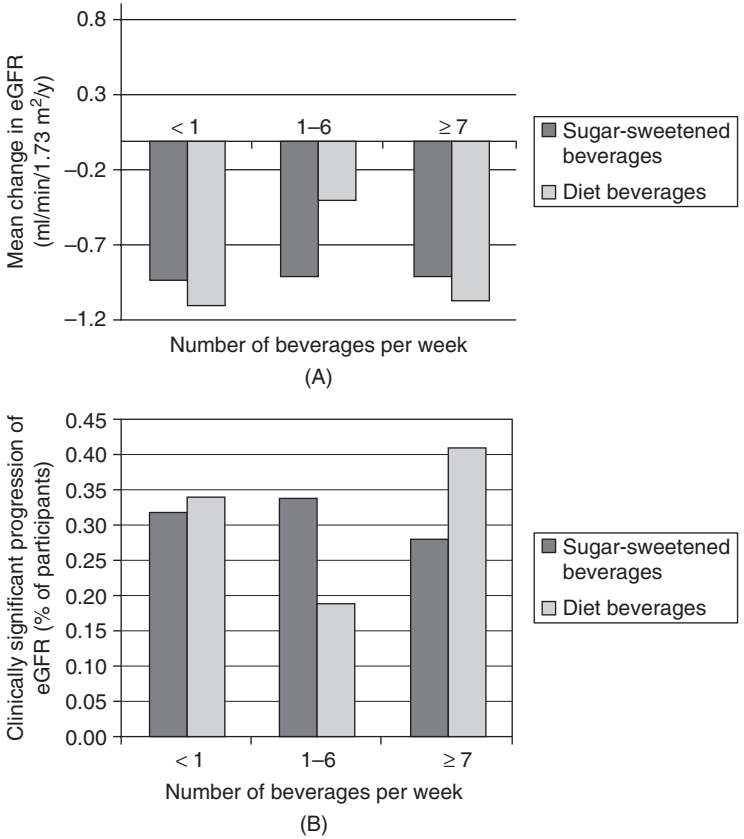


Figure 6.4. Mean change in (A) estimated GFR and (B) clinically significant decline of estimated GFR (defined as greater than 2 ml/min/1.73 m² per year) by sugar-sweetened and diet beverage intake per week among participants in the Multi-Ethnic Study of Atherosclerosis (MESA) with preexistent CKD (n = 447). Represented data reflects univariate relationships; in multivariate analyses, point estimates for diet and regular soda were not significantly different.

Adapted from Bomback AS, Katz R, He K, Shoham DA, Burke GL, Klemmer PJ. Sugar-sweetened beverage consumption and the progression of chronic kidney disease in the Multiethnic Study of Atherosclerosis (MESA). *Am J Clin Nutr*. 2009;90(5):1172–1178.

reduced office and ambulatory blood pressure (with reductions similar in magnitude to most antihypertensive agents) and normalized blood pressure in 86% of patients whose uric acid levels dropped below 5 mg/dl.[67]

Given the preliminary nature of this human data, as well as the potentially serious (albeit extremely rare) adverse effects of allopurinol therapy, xanthine oxidase inhibitor therapy to decrease blood pressure or treat asymptomatic hyperuricemia (assuming higher blood pressure is asymptomatic) cannot be recommended at present. However, it appears reasonable to advise limiting ingestion of foods that are rich in purines and can, if consumed in high quantities, increase serum uric acid levels, such as beer, fatty meats, anchovies, and organ meats (liver, kidneys, sweetbreads). Whether or not regular soft drinks should be included on this list remains debatable.

Exercise

The *Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* (*JNC 7*) advises that all patients with hypertension engage in regular aerobic physical activity, such as brisk walking, for at least 30 minutes per day on most days of the week.[1] This recommendation is based on considerable evidence from clinical trials of hypertensive patients assigned to regular exercise. A meta-analysis of 11 trials, published in 2000, found that progressive resistance exercise results in small reductions in resting systolic and diastolic blood pressure by about 2% and 4%, respectively.[68] A 2002 meta-analysis of 54 trials showed that previously sedentary adults could decrease systolic blood pressure by 3.8 mm Hg (95% CI, 2.7 to 5.0 mm Hg) and diastolic blood pressure by 2.6 mm Hg (95% CI, 1.8 to 3.4 mm Hg) with regular aerobic exercise. All frequencies, intensities, and types of aerobic exercise demonstrated blood pressure-lowering effect on individuals regardless of initial blood pressure (normal or high), weight (normal or overweight), or race/ethnicity (black, white, or Asian).[69]

Studies on the effect of exercise on kidney function itself are limited, and the benefit of physical activity on slowing the progression of CKD has generally been explained by its effects on blood pressure control. In addition, individuals who commit to a regular routine of exercise are presumed to be more likely to commit to other salubrious lifestyle interventions, such as adopting a low-salt diet, abstaining from tobacco, and maintaining body weight in nonmorbid ranges. A recent study in mice by Wang and colleagues,[70] however, sheds light on another potential benefit of exercise for patients with CKD. These investigators had previously shown that CKD induces an increase in muscle protein degradation, mediated by the activation of caspase-3 and the ubiquitin–proteasome proteolytic system, and also suppresses synthesis of new muscle proteins.[71] Using mouse plantaris muscle, they investigated 2 exercise models, one for resistance exercise (muscle overload) and one for endurance training (treadmill running). Both resistance and endurance models slowed the rate of protein breakdown, while only resistance exercise increased protein synthesis. These experiments suggest that regular exercise, in various formats, can directly impact the decline in protein stores and decreased muscle mass that is prevalent in CKD patients and has been associated with increased morbidity and mortality.[72]

Weight Loss

Over the last 3 decades, obesity prevalence has more than doubled among US adults. In the most recent NHANES, 32.2% of US adults had a BMI $\geq$ 30 kg/m^2, meeting the clinical criteria

for obesity.[73] The rising prevalence of obesity has been matched by a parallel increase in the prevalence of metabolic syndrome. This clinical syndrome, marked by abdominal obesity, hypertriglyceridemia, low HDL cholesterol, elevated blood pressure, and impaired insulin sensitivity, is also detectable in roughly 1 in 3 US adults.[74]

Obesity and the metabolic syndrome are risk factors for kidney disease, principally through their links to hypertension and diabetes. The vast majority of hypertensive and diabetic patients are either overweight or obese, and rising BMI is inversely related to control of disease. Among diabetic patients, for example, obesity is associated with poorer control of blood glucose, blood pressure, and cholesterol, heightening the risk for macrovascular (i.e., cardiac) and microvascular (i.e., renal) complications.[75]

Obesity exerts its effect on blood pressure in a myriad of ways. As mentioned earlier in the discussion on salt, obesity and the metabolic syndrome are states of impaired sodium excretion,[28] either due to a natriuretic handicap induced by insulin resistance[29] and/or a hyperactivity of the proximal tubule, with subsequent excessive sodium reabsorption.[30] The impaired sodium excretion in obesity has been postulated as the key step in obesity-associated hypertension.[31,32] Obesity is also frequently accompanied by a hyperactive RAAS.[76–81] Adipocytes express their own fat-based renin-angiotensin system and are consequently able to produce angiotensin II, which in turn stimulates adrenal production of aldosterone.[82,83] Finally, obesity has been characterized as a state of inflammation and oxidative stress, with subsequent endothelial damage and dysfunction leading to blood pressure elevation.[84,85] This is particularly true when obese patients suffer from obstructive sleep apnea,[86] a common comorbid condition.

A growing body of evidence from clinical and epidemiological studies has emerged suggesting that obesity by itself—*independent* of its association with hypertension and/or diabetes—is a key player in renal injuries.[87–92] A multivariate, cross-sectional analysis of NHANES data found a graded association between higher BMI and reduced kidney function (measured by serum cystatin C), with odds ratios (95% CI) of elevated serum cystatin C of 1.46 (1.02–2.10) for overweight (BMI 25.0 to 29.9 kg/m^2), 2.36 (1.56–3.57) for class I obesity (BMI 30.0 to 34.9 kg/m^2), and 2.82 (1.56–5.11) for class II-III obesity (BMI $\geq$ 35.0 kg/m^2).[93] A Turkish study of 110 otherwise healthy obese patients (i.e., nondiabetic, nonhypertensive) showed a significant and independent association between BMI and CKD that may be due to occult inflammation given the correlation between elevated BMI and C-reactive protein levels in this study.[94] A prospective cohort of 8792 healthy Korean men without known risk factors for CKD found that increases in body weight, even when the BMI remained within normal range, were independently associated with increased risk for CKD.[95] Finally, pooled data from the Atherosclerosis Risk in Communities Study and Cardiovascular Health Study demonstrated that waist-to-hip ratio, a preferred anthropomorphic measure of obesity, was an even better predictor than BMI of incident CKD.[96]

The recent study by Serra and others deserves special mention for the novelty of its methods in examining the obesity-CKD relationship.[97] These investigators performed kidney biopsies on 95 extremely obese (i.e., BMI $\geq$ 40) patients without clinical signs of renal dysfunction who were undergoing bariatric surgery. Only about half of these patients were hypertensive, and less than 15% were diabetic. The renal biopsies revealed a variety of glomerular lesions, including increased mesangial matrix, mesangial cell proliferation, podocyte hypertrophy, and glomerulomegaly. The investigators propose that the early lesions found in this study are potential harbingers of future, overt kidney disease.

A number of mechanisms have been proposed as explanations for the obesity-CKD relationship, including chronic inflammation, abnormal vascular remodeling, and renal lipotoxicity.[87] These routes of injury can occur in the absence of diabetes and hypertension, although these comorbidities likely exacerbate the damage. Perhaps the best described mechanism of obesity-induced kidney injury involves the adverse effects of increased body mass and subsequent increased glomerular filtration rate (GFR) per intact nephron. A hyperfiltration injury ensues, as obesity induces, even at normal nephron capacity, the adaptations characteristic of reduced nephron number in CKD.[98] Another proposed mechanism involves adiponectin, a hormone produced by adipocytes that regulates glucose and lipid metabolism. This adipocytokine is decreased in obesity, with levels of adiponectin shown to be inversely related to the degree of albuminuria in obese patients.[99,100] Adiponectin knockout mice have profound proteinuria and, on histology, foot process effacement that both improve with exogenous adiponectin treatments.[101] The end result of these kidney injury pathways can be a proteinuric kidney disease termed *obesity-associated glomerulopathy*, which on histology ranges from glomerulomegaly alone to a secondary focal segmental glomerulosclerosis pattern.[102]

Weight loss, therefore, provides an avenue to slow, halt, and, in some instances, even reverse kidney disease. Much of the benefit of weight loss on kidney function is presumably through reductions in blood pressure. In the PREMIER trial, for example, 810 adult volunteers with systolic blood pressure 120 to 159 mm Hg and/or diastolic blood pressure 80 to 95 mm Hg were randomized to (1) an advice-only group, (2) a multicomponent behavioral intervention that implemented long-established recommendations of weight loss, increased physical activity, and reduced sodium and alcohol intake (the "established" group), or (3) a behavioral intervention that implemented the established recommendations plus Dietary Approaches to Stop Hypertension (DASH) diet (the "established plus DASH" group). Net of advice only, mean systolic BP declined by 3.7 mm Hg for members of the established group ($P < 0.001$) and 4.3 mm Hg for the established plus DASH group ($P < 0.001$). The prevalence of hypertension decreased from a baseline of 38% to 17% in the established group ($P = 0.01$) and to 12% in the established plus DASH group ($P < 0.001$), compared with a decrease to only 26% in the advice-only group.[103,104]

A systematic review evaluating the long-term effects of weight loss on blood pressure in overweight and obese individuals (BMI $\geq$ 28 kg/m^2) suggested that a 10 kg weight loss predicted decreases of 6.0 mm Hg and 4.6 mm Hg in systolic and diastolic blood pressure, respectively, over at least 2 years.[105] A more recent systematic review looking at nonobese subjects found no effect of weight loss on diastolic pressure but a 1 kg:1 mm Hg relationship between weight loss and systolic pressure over follow-up periods of 2 to 3 years.[106] These beneficial effects of diet and weight loss on blood pressure have also been borne out in community-based settings, as demonstrated in the report from Bavikati and others in which 2478 ethnically diverse men and women with prehypertension participated in a community program of therapeutic lifestyle interventions, including exercise training, nutrition counseling, and weight management. Baseline blood pressure decreased, on average, by 6/3 mm Hg, with nearly 40% of subjects normalizing their blood pressure.[107]

The increasing use of weight loss surgery as a treatment of morbid obesity will likely yield a wealth of data on the effects of such drastic weight loss on blood pressure and renal function; thus far, the early studies on this intervention have been very promising. Looking

solely at hypertension, gastric bypass surgery has been reported to cure or improve control of hypertension in up to 70% of patients.[108,109] In a prospective study of 61 extremely obese (BMI $\geq$ 40 kg/m^2) adults undergoing bariatric surgery, mean blood pressure fell from baseline 144.6/85.2 mm Hg to 126.4/75.9 mm Hg 1 year after surgery and 123.4/72.7 mm Hg 2 years after surgery as average weight fell from 150.6 kg to 91.7 kg.[110] A cohort study of 100 patients undergoing laparoscopic Roux-en-Y gastric bypass reported mean 9/7 mm Hg reductions in blood pressure as early as week 1 postoperatively that were maintained over 12 months of follow-up.[111] That the reduction in blood pressure occurred so early, prior to any significant weight loss, raises the issue of a hormonal mechanism being responsible for some of the blood pressure changes. Intentional, nonsurgical weight loss has previously been shown to reduce aldosterone levels,[112,113] and a recent Italian study of laparoscopic gastric banding found a mean, 1-year 10/6 mm Hg decline in blood pressure in 40 hypertensive obese subjects that was accompanied by a concordant decrease in plasma renin activity and aldosterone levels.[114]

As might be expected, large reductions in weight via surgery appear to positively influence renal function. Much of this benefit is likely due to the reductions in blood pressure and improved glycemic control seen postoperatively.[115] Yet, given the evidence presented previously on obesity's nondiabetic and nonhypertensive routes of renal injury, we also speculate that weight loss surgery could have other potentially therapeutic effects on kidney function. An early prospective study showed that bariatric surgery yielded small, but significant, reductions in albuminuria up to 2 years after surgery; this may have been accomplished by a reduction in creatinine clearance from hyperfiltration (mean 140 ml/min preoperatively) to normal levels (mean 118 ml/min at year 2) (**Table 6.2**).[110] Recent retrospective analyses similarly have suggested that weight loss surgery leads to improvements in glomerular filtration rate and reductions in albuminuria in patients with preexisting kidney disease.[116,117] Concomitant reductions in high-sensitivity C-reactive protein levels in these analyses suggest that weight loss surgery reduced overall inflammation and that the renal benefits were not solely due to blood pressure reduction.[118]

Table 6.2. Percentage of extremely obese patients (n = 61) with glomerular hyperfiltration, hypertension, and elevated 24-hour albuminuria/proteinuria before and 24 months after weight loss surgery

	Before Surgery (%)	24 Months After Surgery (%)	Decrease (%)	p-value
Creatinine clearance > 140 ml/min	39.3	16.4	58	0.04
Systolic BP $\geq$ 140 mm Hg	59.0	19.7	67	<0.001
Diastolic BP $\geq$ 90 mm Hg	49.2	11.5	77	0.001
24-h albuminuria $\geq$ 30 mg/day	42.6	14.8	76	<0.001
24-h proteinuria $\geq$ 150 mg/day	47.5	11.5	65	<0.001

Source: Adapted from Navarro-Diaz M, Serra A, Romero R, et al. Effect of drastic weight loss after bariatric surgery on renal parameters in extremely obese patients: long-term follow-up. *J Am Soc Nephrol*. 2006;17 (12, suppl 3):S213–S217.

THERAPY

Hypertension is present in 75–80% of patients with chronic kidney disease (CKD), with the prevalence of hypertension increasing linearly as GFR falls. A number of factors likely contribute to the heavy disease burden of hypertension as kidney function falters, including increased activity of the renin angiotensin aldosterone system, impaired ability to effectively excrete sodium (a natriuretic handicap with subsequent sodium retention), enhanced activity of the sympathetic nervous system, and impaired nitric oxide synthesis and endothelium-mediated vasodilatation. These pathogenic mechanisms explain, in part, why certain antihypertensive medication classes are particularly effective for patients with CKD.

Goal Blood Pressure

Nearly all published guidelines, including the *Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* (*JNC 7*) and the National Kidney Foundation Disease Outcomes Quality Initiative (K/DOQI), recommend goal blood pressure less than 130/80 mm Hg for individuals with CKD (as well as for diabetic patients) to slow progression of kidney disease and reduce cardiovascular risk (**Table 6.3**).[1,2]

Table 6.3. Summary of guidelines and position papers for goal blood pressure in patients with CKD

Group (year)	Goal BP (mm Hg)	Initial Therapy
American Society of HTN (2008)	<130/80	ACE inhibitor/ARB[a,b]
Canadian HTN Society (2007)	≤130/80	ACE inhibitor/ARB
American Diabetes Association (2005)	<130/80	ACE inhibitor/ARB[a]
Japanese HTN Society (2006)	≤130/80	ARB
National Kidney Foundation (2004)	<130/80	ACE inhibitor/ARB[a]
British HTN Society (2004)	≤130/80	ACE inhibitor/ARB
JNC 7 (2003)	<130/80	ACE inhibitor/ARB[a]
ISH/ESC (2003)	<130/80	ACE inhibitor/ARB
Australia-New Zealand (2002)	<130/80	ACE inhibitor
WHO/ISH (1999)	<130/85	ACE inhibitor

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; ESC, European Society of Cardiology; HTN, hypertension; ISH, International Society of Hypertension; *JNC 7, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure*; WHO, World Health Organization.

[a] If BP is substantially above goal, recommended use of initial combination therapy with a thiazide diuretic.

[b] Calcium channel blockers could also be used in combination therapy.

Source: Adapted from Khosla N, Kalaitzidis R, Bakris GL. The kidney, hypertension, and remaining challenges. *Med Clin North Am*. May 2009;93(3):697–715.

Attainment of this goal blood pressure, however, is not often achieved in practice; for example, in the NHANES IV, fewer than 40% of patients with CKD achieved a blood pressure lower than 130/80 mm Hg.[119]

Despite near consensus on this blood pressure target for CKD, the data supporting this goal are not particularly robust. For patients with diabetic nephropathy, data to support the goal of <130/80 mm Hg to minimize cardiovascular risk and slow CKD progression come from post hoc analyses of 3 different trials of patients with moderate to advanced proteinuric kidney disease (eGFR > 60 ml/min/1.73 m^2 and proteinuria >300 mg/day).[120–122] However, all 3 of these trials, at study end, reported a relatively wide range of blood pressure from 120 to 152 mm Hg systolic and 68 to 86 mm Hg diastolic, with a mean blood pressure well above 130/80 mm Hg. In addition, in the Irbesartan Diabetic Nephropathy Trial (IDNT), post hoc analysis suggested that reducing systolic blood pressure below 120/85 mm Hg may have actually increased the risk of all-cause and cardiovascular mortality.[122]

For patients with nondiabetic kidney disease, a meta-analysis of 11 small, randomized, controlled trials (1860 total subjects) suggested that a systolic blood pressure of 110 to 129 mm Hg was associated with the lowest risk for kidney disease progression,[123] but stronger evidence stems from 2 large trials of nondiabetic CKD—the Modification of Diet in Renal Disease (MDRD) study and the African American Study of Kidney Disease and Hypertension (AASK). Both studies enrolled patients with eGFR below 60 ml/min/1.73 m^2 and albuminuria. The MDRD was the first trial to randomize to 2 levels of blood pressure (mean arterial pressure <92 mm Hg vs. 102–107 mm Hg) and follow nephropathy progression. When the trial ended, after a mean follow-up of 2.7 years, the lower blood pressure group saw no advantage in slowing progression of CKD, yet over 8 additional years of follow-up, subjects with baseline proteinuria above 1 g/day randomized to the lower target blood pressure had a slower decline in kidney function and a lower incidence of renal failure compared to those randomized to higher mean pressures.[124] Similarly, the primary analysis of AASK demonstrated that patients randomized to a lower blood pressure target (mean arterial pressure <92 mm Hg) derived no additional benefit on slowing CKD progression over the higher target pressure group (goal mean pressure 102 to 107 mm Hg), but in subgroup analysis, there were slight trends that tended to favor the lower blood pressure goal for subjects with higher proteinuria.[125]

The 10-year follow-up data from the AASK trial are particularly informative when evaluating the goal blood pressure in CKD patients. This trial achieved an average blood pressure difference of 13/8 mm Hg between its treatment groups for a 5-year duration and included an additional 5 years of follow-up during which systolic blood pressure levels averaged less than 135 mm Hg in the entire low pressure cohort. Even with this level of control, however, about 65% of the low target cohort had progression of CKD, albeit markedly slowed.[126] A potential reason for this progression despite apparent good control of hypertension was the discovery of masked and nocturnal hypertension that was missed by routine office measurement but ascertained by 24-hour ambulatory blood pressure monitoring.[127] Thus, routine blood pressure measurements are likely not adequate for determining risk of CKD progression in patients with preexistent kidney disease.

The data currently provide the most support for a goal blood pressure of <130/80 mm Hg in the subgroup of patients with proteinuria and CKD. Data from the MDRD and AASK studies also suggest that this benefit in patients with proteinuric kidney disease, achieved with

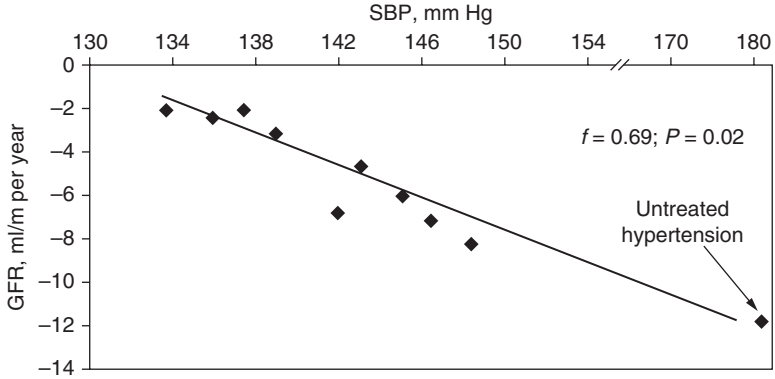
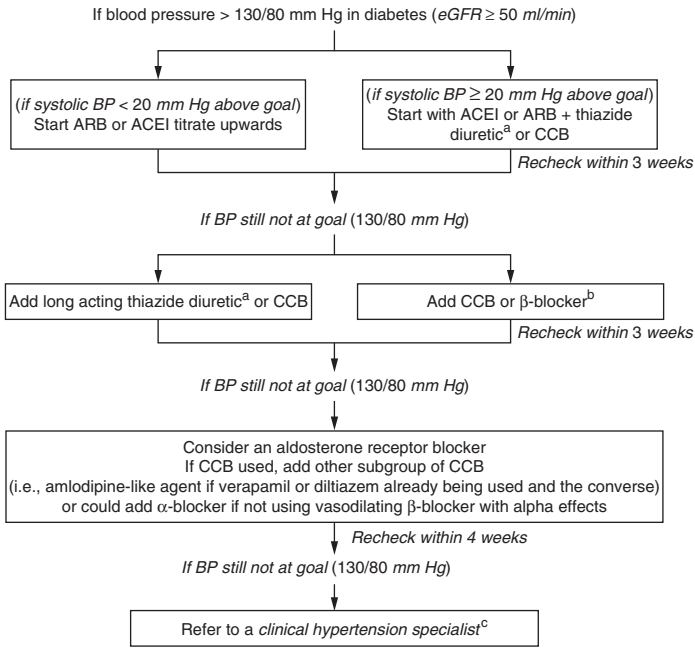


Figure 6.5. The relationship between achieved level of blood pressure and rate of decline in renal function in renal outcome trials. Note that all studies that showed significant differences in outcomes had baseline proteinuria > 300 mg/day.

mean blood pressures from 127 to 132 mm Hg over 77 to 80 mm Hg, nonetheless takes, on average, 5 years to become apparent. Taken together, despite the consensus of guideline recommendations, the current medical literature reaches the following conclusions: In patients with baseline GFR values below 60 ml/min/1.73 m^2, those with blood pressures that *approach* but do not necessarily *meet* the goal of 130/80 mm Hg have slower rates of kidney function decline, and this benefit is most pronounced among those with advanced, proteinuric CKD (**Figure 6.5**).[128] Indeed, the current data support only the following observation: A blood pressure $<$130/80 mm Hg slows nephropathy progression to a greater extent than a blood pressure around 140/90 mm Hg in people with an eGFR $<$ 45 ml/min *and* a urinary albumin excretion rate $>$300 mg/day. This observation is not true if albuminuria is not present or if it is in a low amount (i.e., microalbuminuria). Additionally, theses benefits are seen after 4 or more years of follow-up and not during shorter durations of follow-up.[128,129] This issue will be taken up again in Chapter 7.

RAAS Blockade

Increased activity of the RAAS, likely due to regional ischemia induced by kidney injury-induced scarring, is considered to be a key player in the pathogenesis of hypertension in kidney disease. Blockade of the RAAS has therefore emerged as a key treatment option to slow the progression of CKD, particularly proteinuric CKD, and consequently is suggested by nearly all published guidelines as first-line antihypertensive therapy in CKD for both renal and



ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BP, blood pressure; CCB, calcium-channel blocker; eGFR, estimated glomerular filtration rate.

[a] Chlorthalidone is the suggested thiazide diuretic as this was used in clinical trials and forms the basis for the cardiovascular outcome data.

[b] Vasodilating beta-blockers (e.g., carvedilol, nebivolol) have a better tolerability profile and less metabolic consequences as compared to older agents such as atenolol.

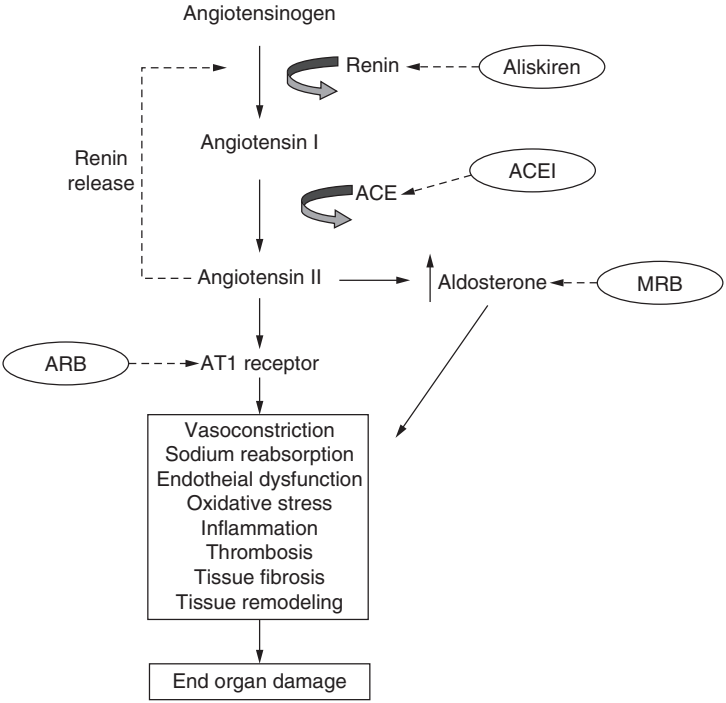
[c] Specialists can be found at http://www.ash-us.org/specialist_program/directory.htm.

Figure 6.6. A suggested approach to achieve goal blood pressure in patients with diabetes or albuminuria.

Source: Bakris GL and Sowers JR. ASH position paper: treatment of hypertension in patients with diabetes—an update. *J Clin Hypertens (Greenwich)*. 2008;10(9):707–715.

cardiac protection (Table 6.3, **Figure 6.6**). Proteinuria is, next to elevated blood pressure, a major risk for progression to end stage renal disease in both diabetic and nondiabetic CKD, and RAAS-blocking drugs protect against progressive loss of renal function by reducing blood pressure and proteinuria.

The RAAS is a major neurohormonal pathway that helps regulate blood pressure as well as fluid and electrolyte balance **(Figure 6.7)**.[130] A hyperactive RAAS results in potent vasoconstriction



ACE, angiotensin-converting enzyme; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; AT1, MRB, mineralocorticoid receptor blocker

Figure 6.7. The renin angiotensin aldosterone system and currently available therapeutic approaches to its control. Black arrows show stimulation or sequence of events; dotted lines depict inhibition.

Reprinted with permission from Ruilope L, Kjeldsen SE, de la Sierra A, et al. The kidney and cardiovascular risk—implications for management: a consensus statement from the European Society of Hypertension. *Blood Press.* 2007;16(2):72–79 from Taylor & Francis Ltd.

and sodium retention, thus raising blood pressure and presenting an optimal treatment target. Blockade of the RAAS has, until recently, been accomplished by inhibiting the formation of angiotensin II (ANG II) with angiotensin-converting enzyme (ACE) inhibitors, blocking the actions of ANG II at the ANG II type I (AT_1) receptor with ARBs, or blocking the effects of

aldosterone with mineralocorticoid receptor blockers (MRBs). Aliskiren, a recently approved direct renin inhibitor (DRI) that binds to renin and inhibits its ability to convert angiotensinogen to angiotensin I (ANG I), offers yet another route of RAAS inhibition.

The first trial to demonstrate a benefit of ACE inhibitors in CKD was the Captopril Nephropathy Trial in type 1 diabetics, which showed a nearly 75% risk reduction in doubling of serum creatinine and in the combined outcome of death and end stage renal disease in subjects treated with captopril compared to subjects treated with placebo. This beneficial effect, however, was limited to subjects whose serum creatinine levels were >2 mg/dl; in subjects whose creatinine levels were <1 mg/dl, ACE inhibition yielded no significant benefit when similar blood pressures were achieved.[131] The Ramipril Efficacy in Nephropathy study also demonstrated a 62% reduction in kidney disease progression (defined by changes in GFR) in subjects with creatinine values above 2 mg/dl and more than 3 g/day proteinuria compared with a 22% reduction in subjects with albuminuria alone.[132] Yet, while early clinical trial data suggested that ACE inhibitors provide additional, blood pressure–independent protection against nephropathy progression, larger clinical trials and meta-analyses have not borne this out and instead have concluded that achieved blood pressure, rather than medication class, is the key intervention.[123,133] This difference may be explained, in part, by different subject populations, as the early trial data found benefit specifically in advanced CKD, namely GFR <50 ml/min/1.73 m^2 accompanied by >500 mg/day proteinuria. In earlier stages of kidney disease, the blood pressure–independent effects of ACE inhibitors may not be as potent. Unfortunately, clinical practice databases indicate that these agents are being given with a very low frequency to patients with advanced CKD, who would likely garner the most benefit.

ARBs emerged as an alternative to ACE inhibitors due to their improved side effect profile, with lower incidence of cough (presumably they do not affect bradykinin), angioedema, taste disturbances, and hyperkalemia.[134] The Reduction of Endpoints in Non-insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL)[135] study and the IDNT[136] both used a primary composite outcome of doubling of baseline serum creatinine, onset of end stage renal disease, or death, and both showed that in advanced CKD, using an ARB to reduce blood pressure led to a greater decrease in nephropathy progression than using other antihypertensive agents (e.g., calcium channel blockers, beta-blockers). Data directly comparing renal outcomes of ARBs and ACE inhibitors are currently limited to one trial that was underpowered and not in a cohort that would yield a meaningful outcome on CKD progression (i.e., subjects had early rather than advanced kidney disease, with eGFR > 70 ml/min/1.73 m^2 an inclusion criterion); hence, no difference was noted between the 2 classes over 5 years of follow-up.[137] The Combination Treatment of Angiotensin-II Receptor Blocker and Angiotensin-Converting Enzyme Inhibitor in Non-diabetic Renal Disease[138] trial also compared these classes but major data inconsistencies have been reported.[139,140]

Given the benefits of using ACE inhibitors and ARBs in established kidney disease, a number of recent studies have examined whether these agents could prevent incipient kidney disease if used early in diabetes or heart disease. The results have thus far shown no apparent advantage over placebo. A 5-year study by Mauer and others found that early blockade of the RAAS with either an ACE inhibitor or ARB in patients with type 1 diabetes, while slowing the progression of retinopathy, did not protect against the progression of nephropathy on biopsy findings and measurements of urinary albumin excretion.[141] In the Telmisartan Randomised Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease, 5927 subjects with vascular disease but without macroalbuminuria saw no important difference in the composite

renal outcome of dialysis or doubling of serum creatinine with telmisartan versus placebo.[142] And the results from 3 randomized trials of the Diabetic Retinopathy Candesartan Trials program showed that ARB therapy for a median of 4.7 years did not prevent microalbuminuria in mainly normotensive patients with diabetes.[143]

The *JNC 7* recommends use of aldosterone antagonists—specifically, the MRBs spironolactone or eplerenone—for treating hypertension in patients with advanced heart failure and postmyocardial infarction. This recommendation stems from the findings from 2 landmark heart failure clinical trials, the Randomized Aldactone Evaluation Study (RALES)[144] and the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS),[145] in which MRB therapy, compared to placebo, significantly lowered the risk of all-cause mortality (by 30% in the RALES and by 15% in the EPHESUS). However, the role of these medications continues to expand. Spironolactone has recently emerged as an effective therapy for resistant hypertension (blood pressure above goal despite use of 3 or more antihypertensive agents of different classes),[146] yielding a dramatic 21.8/9.5 mm Hg reduction in blood pressure for 1411 participants in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) who received the MRB mainly as a fourth-line agent for uncontrolled blood pressure (**Figure 6.8**).[147] Additionally, a number of small studies, which have been systematically

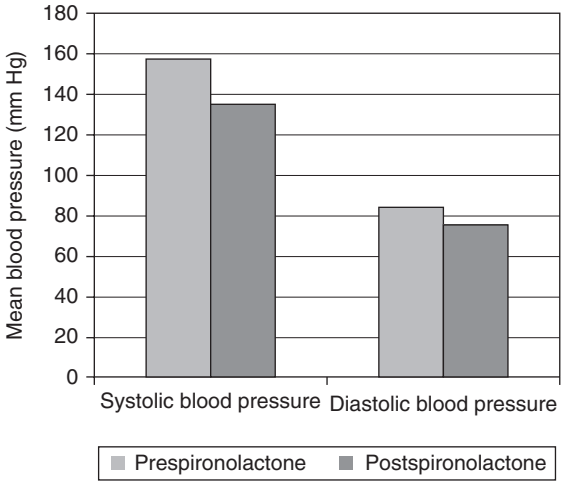


Figure 6.8. Mean blood pressure before (pre-) and during (post-) spironolactone treatment in 1411 ASCOT participants with resistant hypertension. Overall, systolic blood pressure decreased by 21.9 mm Hg (95% CI 20.8–23.0), and diastolic blood pressure decreased by 9.5 mm Hg (95% CI 9.0–10.1).

Adapted from Chapman N, Dobson J, Wilson S, et al. Effect of spironolactone on blood pressure in subjects with resistant hypertension. *Hypertension.* 2007;49(4):839–845.

reviewed by 2 sets of authors,[148,149] have demonstrated a significant antiproteinuric effect of MRB therapy given either alone or in combination with other RAAS-blocking drugs. The long-term benefits of MRB therapy on renal function, as well as the safety of these drugs in advanced CKD, have yet to be determined.

Renin has long been regarded as the logical point to inhibit the RAAS because it is the first and rate-limiting step in the cascade and is highly selective for its substrate, angiotensinogen.[150,151] Aliskiren is the first and only direct renin inhibitor (DRI) currently approved for the treatment of hypertension. Studies in hypertensive patients have demonstrated that aliskiren is a well-tolerated, effective, and long-acting antihypertensive agent when used alone[152–154] or in combination with other antihypertensive drugs, including hydrochlorothiazide,[155] amlodipine,[156] ramipril,[157] and valsartan,[158] but a role distinct from ACE inhibitors or ARBs has yet to be elucidated for the DRI. Presently, the data available on using aliskiren in CKD patients comes from the Aliskiren in the Evaluation of Proteinuria in Diabetes trial,[159] in which 599 patients with hypertension and early type 2 diabetic nephropathy (mean estimated GFR 67.6 ml/min/1.73 m^2 and mean urinary albumin:creatinine ratio 532.9 mg/g), maintained on losartan, were randomized to receive a 6-month treatment with aliskiren or placebo. After 3 months of treatment with aliskiren (150 mg/d), the urinary albumin to creatinine ratio had decreased by 11% compared with placebo ($P = 0.02$); increasing the dose of aliskiren to 300 mg/d caused a further decrease in the urinary albumin-to-creatinine ratio to 20% ($P < 0.001$ vs. placebo) at study end (**Figure 6.9**). This reduction in proteinuria occurred in the presence of a small but nonsignificant decrease in blood pressure (2/1 mm Hg), suggesting that addition of aliskiren to losartan in this diabetic population had potential renoprotective effects independent of blood pressure. However, we must await the results of the Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Endpoints to determine how the effects of DRI on slowing nephropathy progression in patients with advanced CKD (inclusion criteria includes persistent micro- or macroalbuminuria and an estimated GFR of $\geq$30 and $<$60 mL/min/1.73 m^2) compares to those of ACE inhibitors or ARBs.[160]

Some specific exceptions hold about the use and potential benefits of RAAS blockade in CKD. First, there are no data that support the use of RAAS blockade to slow nephropathy progression in individuals above 65 years of age.[161] Additionally, as mentioned earlier, there are no unique benefits of RAAS blockers on CKD progression among patients with low eGFRs (i.e., $<$60 ml/min) and no albuminuria.[128,162,163] Thus, based on the current evidence, RAAS blockade should not be automatically added to everyone with CKD unless albuminuria is present.

Despite these exceptions, since the introduction of ACE inhibitors in the early 1980s and ARBs in the mid-1990s as antihypertensive therapies, pharmacologic blockade of the RAAS has become one of the most effective and widespread therapeutic approaches in the management of cardiovascular and kidney disease. However, significant numbers of patients with chronic heart and kidney disease progress despite this standard therapy. Incomplete blockade of the RAAS at recommended doses may explain this observation.[164,165] Therefore, one strategy to improve the efficacy of RAAS blockade is to combine agents. This combination strategy of dual RAAS blockade, which to date has principally been achieved with ACE inhibitors and ARBs but can also be achieved with DRI or MRB therapy, will be taken up in depth in Chapter 7.

Many physicians have observed increases in serum creatinine after initiation of RAAS blockade, attributing the rise to the renal hemodynamics of these agents. While partially true, GFR will commonly fall after properly reducing blood pressure in someone who has failed

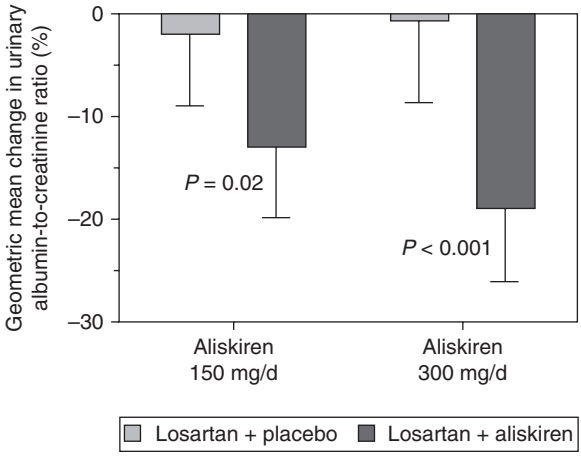


Figure 6.9. Effect of aliskiren combined with losartan on the urinary albumin to creatinine ratio in patients with type 2 diabetes and nephropathy. Patients received losartan (100 mg/d) throughout the study and were randomized to receive placebo or 150 mg/d of aliskiren for 3 months followed by 300 mg/d for an additional 3 months.

Data from 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):2433–2446.

to have it controlled for years, regardless of antihypertensive drug class. In studies evaluating changes in serum creatinine over a period of 6 months after blood pressure has been reduced, creatinine can increase from 0% to 20% for all antihypertensives and from 10% to 35% if RAAS blockade is used. Creatinine increases of up to 45% in the RENAAL and IDNT studies occurred, yet the agents continued to confer benefit over the long term. Clearly, these creatinine increases over time result in better renal outcomes and should not be a deterrent to their use in advanced nephropathy. We suggest that only 2 factors should limit appropriate use of RAAS blockade: (1) hyperkalemia (i.e., serum potassium above 6 mEq/L), in which case the dose should be reduced, or (2) a >40% increase in serum creatinine within the first 2 months after blood pressure control has been achieved, which would suggest intrarenal vascular disease and a relative contraindication to the drug.[166,167]

Diuretics

As renal function deteriorates, the kidney's ability to effectively excrete sodium declines. Sodium retention can be clinically apparent, in the form of lower extremity edema or pulmonary

congestion, but volume expansion can also be occult and not easily detected. This occult volume expansion of renal dysfunction is actually a misnomer, as the natriuretic handicap of CKD is almost always manifested in the form of elevated blood pressure.[168] The salt-excreting deficiency and ensuing extracellular volume expansion, even when insufficient to induce edema, provides the basis for treating hypertension in CKD with diuretics. Indeed, diuretics should be pushed in patients with CKD until the blood pressure goal is reached or the patient has attained a euvolemic weight, below which further fluid loss leads to orthostatic symptoms or to decreased renal perfusion as evidenced by an otherwise unexplained elevation in the blood urea nitrogen and/or serum creatinine concentrations.

Thiazide diuretics gained a renewed importance in treating hypertension after the publication of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT),[169] in which patients were randomized to treatment with chlorthalidone, lisinopril, or amlodipine. No significant difference was observed between amlodipine and chlorthalidone for the primary outcome (fatal coronary heart disease or nonfatal myocardial infarction) or for the secondary outcomes of all-cause mortality, combined coronary heart disease, stroke, combined cerebrovascular disease, angina, coronary revascularization, peripheral arterial disease, cancer, or end stage renal disease. No significant difference was observed between lisinopril and chlorthalidone for the primary outcome or for the secondary outcomes of all-cause mortality, combined coronary heart disease, peripheral arterial disease, cancer, or end stage renal disease, but the lisinopril group had a 15% higher risk for stroke ($P = 0.02$) and a 10% higher risk of combined cerebrovascular diseases ($P < 0.001$) (**Figure 6.10**).[169] Similar outcomes were observed in the subset of ALLHAT patients with an estimated GFR $<$ 60 ml/min/1.73 m^2, including no difference in the development of end stage renal disease.[133] Chlorthalidone, notably, was associated with modestly lower blood pressures throughout the trial compared to the amlodipine and lisinopril arms, which may explain, in part, the results.

Hydrochlorothiazide is used more commonly in current clinical practice, and *JNC 7* makes no specific recommendation about particular thiazide diuretics. Nonetheless, strong consideration should be given to using chlorthalidone over hydrochlorothiazide, given that the major outcome trials supporting diuretics used chlorthalidone.[169–171] Chlorthalidone is likely more potent because of its longer half-life (44 hours for chlorthalidone vs. 12 hours for hydrochlorothiazide), which translates into an additional 7 mm Hg reduction in systolic blood pressure when substituted for hydrochlorothiazide.[172,173] This enhanced blood pressure-lowering effect is manifested most clearly in 24-hour ambulatory blood pressure monitoring (ABPM) and is mostly due to superior control of nocturnal pressure (**Figure 6.11**).[174] The growing importance of nocturnal blood pressure levels as a factor in cardiovascular target organ damage[175–177] and progressive kidney function loss[178] lend further support to preferentially using chlorthalidone over hydrochlorothiazide. We note, however, that a meta-analysis of 5 placebo-controlled trials of low-dose diuretics concluded that major health outcomes for chlorthalidone and other thiazide-like drugs appear to be similar (**Table 6.4**).

A potential side effect seen with thiazide diuretics is an increased risk for hyperglycemia and hypokalemia. These adverse events are believed to be linked, with hypokalemia leading to glucose intolerance through impairment of potassium-dependent insulin release in response to a glucose load.[179] A post hoc analysis of data from 3790 nondiabetic participants in the Systolic Hypertension in Elderly Program trial demonstrated that each 0.5 mEq/l decrease in serum potassium during the first year of chlorthalidone therapy was independently associated

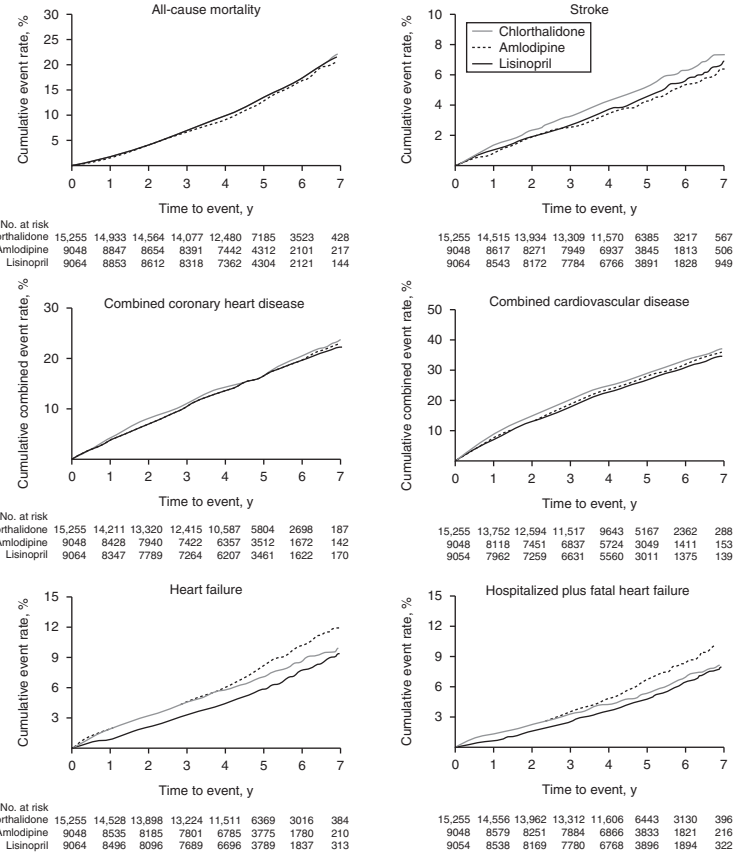
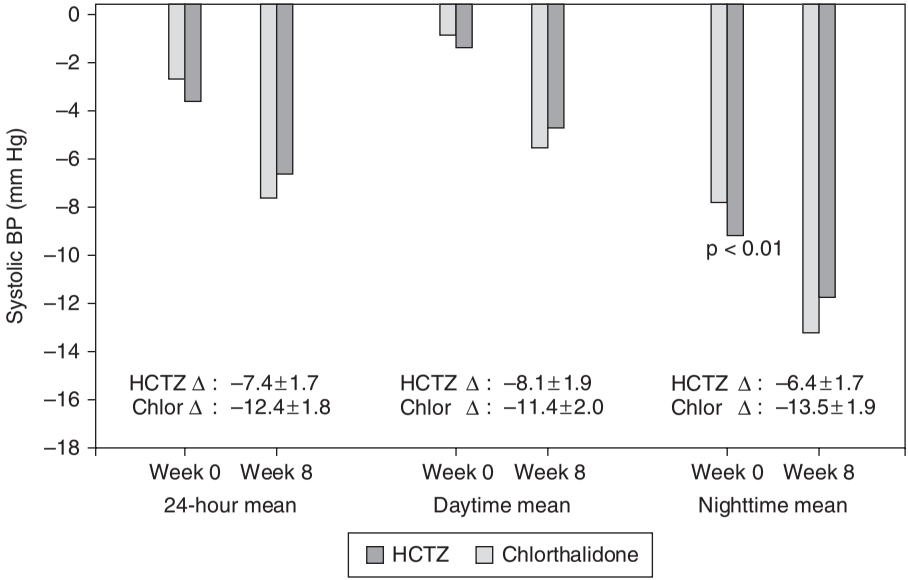


Figure 6.10. Cumulative event rates for all-cause mortality, stroke, combined coronary heart disease, combined cardiovascular disease, heart failure, and hospitalized plus fatal heart failure by treatment group (amlodipine, lisinopril, and chlorthalidone) in the ALLHAT.



Baseline BP during 24-hour and daytime ranged between 138 and 144. Nighttime values were between 120 and 125.

Figure 6.11. Mean 24-hour, daytime, and nighttime ambulatory systolic blood pressures, with change from baseline, in 30 patients treated with chlorthalidone or hydrochlorothiazide.

Adapted from Ernst ME, Carter BL, Goerdt CJ, et al. Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. *Hypertension*. 2006;47(3):352–358.

Table 6.4. Direct and indirect comparisons of chlorthalidone and nonchlorthalidone diuretics for 6 major outcomes based on placebo-controlled trials

	Direct Comparison RR (95% CI)		Indirect Comparison SI (95% CI)[a]
	Chlorthalidone vs. Placebo	***Nonchlorthalidone vs. Placebo***	***Chlorthalidone vs. Nonchlorthalidone***
Coronary disease	0.74 (0.58–0.95)	0.72 (0.54–0.95)	1.03 (0.71–1.48)
Stroke	0.64 (0.51–0.80)	0.71 (0.60–0.85)	0.90 (0.70–1.17)
Heart failure	0.53 (0.39–0.73)	No data	No data
CVD events	0.70 (0.61–0.80)	0.76 (0.66–0.87)	0.92 (0.76–1.11)
CVD mortality	0.80 (0.61–1.04)	0.79 (0.65–0.94)	1.01 (0.74–1.39)
Total mortality	0.89 (0.75–1.06)	0.91 (0.79–1.03)	0.98 (0.79–1.21)

CI, confidence interval; CVD, cardiovascular disease; RR, relative risk; SI, synergy index.

[a] SI < 1 suggests that chlorthalidone is superior to nonchlorthalidone diuretics for that outcome; SI > 1 suggests that chlorthalidone is inferior to nonchlorthalidone diuretics for that outcome.

Source: Adapted from Psaty BM, Lumley T, Furberg CD. Meta-analysis of health outcomes of chlorthalidone-based vs nonchlorthalidone-based low-dose diuretic therapies. *JAMA*. 2004;292(1):43–44.

with a 45% higher adjusted diabetes risk.[180] However, the increase in glucose at currently used doses is quite small, and the risk of new onset diabetes is decreased further when combined with an ACE inhibitor or ARB, which tend to raise serum potassium levels.[181,182] Moreover, no study to date has been able to link thiazide-induced hyperglycemia to worse cardiac or renal outcomes.

Thiazide diuretics in conventional doses are most effective in patients with an estimated GFR $>$ 50 ml/min/1.73 m^2 and are generally considered ineffective as monotherapy when GFR falls below 30 ml/min/1.73 m^2. Therefore, when a diuretic is given to treat hypertension and/or edema in patients with advanced CKD, a loop diuretic should be used. Typically, the loop diuretics should be dosed at least twice daily unless using the longer-acting torsemide. Diuretic resistance is a commonly encountered problem and relates to underdosing, severe hypoalbuminemia, or heart failure. Classically, the approach to these refractory patients involves either increasing the dose of the loop diuretic or combining the loop diuretic with a diuretic that acts more distally in the nephron, such as a thiazide. Because chronic exposure to loop diuretics leads to hypertrophy of the epithelial sodium channel in the cortical collecting duct,[183] consideration should be given to using a potassium-sparing diuretic, such as amiloride, with a loop diuretic.

Given the importance of lowering proteinuria in both diabetic and nondiabetic CKD, which is principally accomplished by the staple therapy of RAAS blockade in these conditions, we also note that diuretics have been shown to enhance the responses of proteinuria and blood pressure to ACE inhibitors and ARBs.[12,13,184] This enhanced antiproteinuric effect of RAAS blockade is similar to that seen with salt restriction,[185] highlighting that successful diuresis can

reduce extracellular volume, which may be construed as an anti-inflammatory intervention.[168] Thus diuretics, in combination with RAAS blockade, should be considered first-line agents in treating hypertension in CKD.

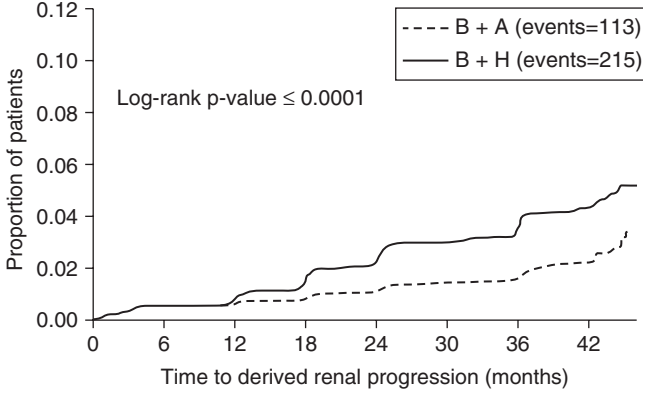
Calcium Channel Blockers

Calcium channel blockers (CCBs) are also effective in treating hypertension in CKD. When used in patients with nonproteinuric CKD, both dihydropyridine CCBs (amlodipine, nifedipine) and nondihydropyridine CCBs (verapamil, diltiazem) are effective in lowering blood pressure and reducing the rate of cardiovascular events in high-risk populations.[186] These agents have demonstrated particular efficacy in cardiovascular risk reduction when paired with an ACE inhibitor. The International Verapamil-Trandolapril Study, a randomized, open-label study of more than 20,000 patients with hypertensive coronary artery disease, demonstrated that a regimen based on CCB plus ACE inhibitor effectively reduced cardiovascular outcomes and all-cause mortality.[187] More recently, the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) study randomized 11,506 patients with hypertension at high risk for cardiovascular events to receive either benazepril plus amlodipine or benazepril plus hydrochlorothiazide.[188] This trial, despite similar blood pressure reductions in both arms (both office and 24-hour measurements), reported an approximately 20% lower risk of primary outcome events—a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, hospitalization for angina, resuscitation after cardiac arrest, and coronary revascularization—in subjects treated with the benazepril-amlodipine combination. Moreover, the prespecified analysis of the CKD outcomes from this trial demonstrated fewer people progressing to ESRD and doubling of creatinine if they were randomized to the ACE inhibitor/CCB combination (**Figure 6.12**).

In patients with proteinuric kidney disease, dihydropyridine CCBs do not reduce albuminuria to the same extent as do nondihydropyridine CCBs. In a quantitative systematic review of randomized clinical trials with at least 6 months of treatment of either a dihydropyridine or nondihydropyridine CCB, percentage change in proteinuria, after adjustment for sample size and study length, for dihydropyridine CCBs and nondihydropyridine CCBs was +2% and −30%, respectively ($P < 0.01$), despite essentially equal reductions in systolic blood pressure.[189] For this reason, the K/DOQI blood pressure guidelines recommend that dihydropyridine CCBs not be used alone to lower blood pressure in people with CKD and albuminuria >300 mg/day.

When dihydropyridine calcium antagonists are added to a regimen already containing RAAS blockers or used simultaneously with a RAAS blocker to lower blood pressure, the effects on albuminuria reduction differ from their use alone. This is exemplified by 2 studies. A prospective study of 304 subjects with hypertension and diabetic nephropathy, treated for 36 weeks with an ACE inhibitor added to either a dihydropyridine (amlodipine) or nondihydropyridine (verapamil) CCB, found no statistically significant difference between groups in the change in albuminuria.[190] The retrospective analysis of the RENAAL trial, discussed earlier, also showed that ARB combined with dihydropyridine CCB can yield substantial proteinuria reductions.[121]

Taken together, the literature advocates aggressive use of both classes of CCBs to achieve blood pressure reduction in patients without proteinuric CKD, particularly in conjunction with ACE inhibitors (or other RAAS-blocking drugs). In patients with advanced proteinuric nephropathy,



Number at risk

B + A	5743	5578	5452	5336	5203	5022	3016	1559
B + H	5762	5576	5459	5307	5139	4936	2956	1506

Figure 6.12. Kaplan-Meier curves for time to the renal progression end point in the ACCOMPLISH trial. Renal progression was defined in this trial as doubling of serum creatinine, achievement of end stage renal disease, need for dialysis, or GFR falling to <15 ml/min. B, benazepril; A, amlodipine; H, hydrochlorothiazide.

Bakris GL, Sarafidis PA, Weir MR, Dahlöf B, Pitt B, Jamerson K, Velazquez EJ, Staikos-Byrne L,Kelly RY, Shi V, Chiang YT, Weber MA, for the ACCOMPLISH Trial investigators. Renal outcomes with different fixed-dose combination therapies in patients with hypertension at high risk for cardiovascular events (ACCOMPLISH): a prespecified secondary analysis of a randomised controlled trial. *Lancet*. 2010;375:1173–1181.

nondihydropyridine CCBs are advanced by guidelines, but dihydropyridine CCBs can also be used in combination with ACE inhibitors or ARBs to maximally reduce blood pressure and slow nephropathy progression.[2] The results of the ACCOMPLISH trial raise the possibility that initiating therapy with the combination of amlodipine (or, presumably, another dihydropyridine CCB) plus a RAAS-blocking drug provides unique beneficial effects compared with traditional monotherapy. This is hypothesized to be true because of the additive, possibly synergistic effects of amlodipine with benazepril on the vascular endothelium, and specifically the increased availability of vascular endothelial nitric oxide.[191–194] In that instance, however, we'd expect an enhanced albuminuria-lowering effect of ACE inhibitors or ARBs with addition of amlodipine, which has not been the case.[195] This lack of effect, however, may be due to increased vascular permeability exhibited by amlodipine and elimination of renal autoregulation.[195,196]

In patients with stage 1 hypertension, proteinuria, and CKD, the initial agents to control hypertension should therefore still be a diuretic and a RAAS-blocking drug. However, based on the recent CKD outcome data from the ACCOMPLISH trial, those with stage 2 hypertension

and CKD appear to achieve greater benefit by initiating therapy with an ACE inhibitor/CCB combination rather than an ACE inhibitor/diuretic (Figure 6.12). As many CKD patients will require more than 2 agents to control their blood pressure, adding a CCB has emerged as the next clear choice.

Beta-Blockers

Clinicians have become increasingly reluctant to use beta-blockers in the treatment of hypertension, and recent guidelines (e.g., British Hypertension Society and the National Institute for Health and Clinical Excellence) have specifically not recommended their use for first-line therapy despite their well-documented efficacy in lowering blood pressure. This reversal in philosophy is primarily due to data focused on atenolol rather than the entire class of drugs. Clinical trials have also uncovered that the first-generation beta-blockers, such as atenolol and metoprolol, have a significant, adverse metabolic profile and increase the risk for insulin resistance.[197–199] Additionally, recent studies demonstrate that excessive reduction in heart rate may pose a problem with beta-blockers, although more than 80% of the studies cited used atenolol.[200]

The Losartan Intervention for Endpoint Reduction in Hypertension study found that losartan-based regimens prevented more cardiovascular morbidity and death than atenolol-based regimens despite similar blood pressure reduction; most of the effect was seen in differential rates of fatal and nonfatal stroke.[201] The ASCOT-BPLA, referenced earlier, was a multicenter, prospective, randomized, controlled trial of 19,257 patients with hypertension, aged 40–79 years with at least 3 other cardiovascular risk factors, who were assigned either amlodipine adding perindopril as required (amlodipine-based regimen; n = 9639) or atenolol adding bendroflumethiazide as required (atenolol-based regimen; n = 9618).[202] Subjects on the amlodipine-based regimen fared better than subjects on the atenolol-based regimen regarding nearly every outcome under study (**Figure 6.13**), including all-cause mortality, cardiovascular death, myocardial infarction, stroke (fatal and nonfatal), and new-onset renal impairment. The Conduit Artery Function Evaluation substudy of ASCOT examined the impact of the 2 different blood pressure–lowering regimens on central aortic pressures and hemodynamics.[203] Despite similar brachial systolic blood pressures between treatment groups, there were substantial reductions in central aortic pressures with the amlodipine regimen not seen in the atenolol regimen, reducing the risk for cardiovascular events and development of renal impairment. Thus, differences in central aortic pressures, a surrogate measurement of extracellular volume expansion, may be a potential mechanism to explain the different clinical outcomes between the amlodipine- and atenolol-based treatment arms in ASCOT.

In contrast, a recent meta-analysis of 147 randomized trials of blood pressure–lowering drugs demonstrated that beta-blockers had enhanced efficacy, beyond mere blood pressure reduction, in preventing recurrent cardiac events in individuals with a history of coronary heart disease, reducing risk by about twice the rate of other antihypertensive drugs.[204] As all advanced CKD patients have an increase in sympathetic activity and a high cardiovascular event rate, the available data clearly suggest a benefit of beta-blockers for these patients, and the drug class, currently underutilized, should be prescribed more often to reduce cardiovascular risk.[200]

The emergence of newer beta-blockers—for example, the combined alpha- and beta-blocker, carvedilol, and the beta-1 vasodilating agent, nebivolol—may expand the role for these agents

	Amlodipine-based regimen (n=9639)		Atenolol-based regimen (n=9618)			
	Number (%)	Rate per 1000	Number (%)	Rate per 1000	Unadjusted HR (95% CI)	p
Primary end points						
Nonfatal myocardial infarction (including silent) + fatal CHD	429 (4%)	8.2	474 (5%)	9.1	0.90 (0.79-1.02)	0.1052
Secondary end points						
Nonfatal myocardial infarction (excluding silent) + fatal CHD	390 (4%)	7.4	444 (5%)	8.5	0.87 (0.76-1.00)	0.0458
Total coronary end point	753 (8%)	14.6	852 (9%)	16.8	0.87 (0.79-0.96)	0.0070
Total cardiovascular events and procedures	1362 (14%)	27.4	1602 (17%)	32.8	0.84 (0.78-0.90)	<0.0001
All-cause mortality	738 (8%)	13.9	820 (9%)	15.5	0.89 (0.81-0.99)	0.0247
Cardiovascular mortality	263 (3%)	4.9	342 (4%)	6.5	0.76 (0.65-0.90)	0.0010
Fatal and nonfatal stroke	327 (3%)	6.2	422 (4%)	8.1	0.77 (0.66-0.89)	0.0003
Fatal and nonfatal heart failure	134 (1%)	2.5	159 (2%)	3.0	0.84 (0.66-1.05)	0.1257
Tertiary end points						
Silent myocardial infarction	42 (0.4%)	0.8	33 (0.3%)	0.6	1.27 (0.80-2.00)	0.3089
Unstable angina	73 (1%)	1.4	106 (1%)	2.0	0.68 (0.51-0.92)	0.0115
Chronic stable angina	205 (2%)	3.9	208 (2%)	4.0	0.98 (0.81-1.19)	0.8373
Peripheral arterial disease	133 (1%)	2.5	202 (2%)	3.9	0.65 (0.52-0.81)	0.0001
Life-threatening arrhythmias	27 (0.3%)	0.5	25 (0.3%)	0.5	1.07 (0.62-1.85)	0.8009
Development of diabetes mellitus	567 (6%)	11.0	799 (8%)	15.9	0.70 (0.63-0.78)	<0.0001
Development of renal impairment	403 (4%)	7.7	469 (5%)	9.1	0.85 (0.75-0.97)	0.0187
Post-hoc end points						
Primary end point + coronary revascularisation procedures	596 (6%)	11.5	688 (7%)	13.4	0.86 (0.77-0.96)	0.0058
Cardiovascular death + myocardial infarction + stroke	796 (8%)	15.4	937 (10%)	18.4	0.84 (0.76-0.92)	0.0003

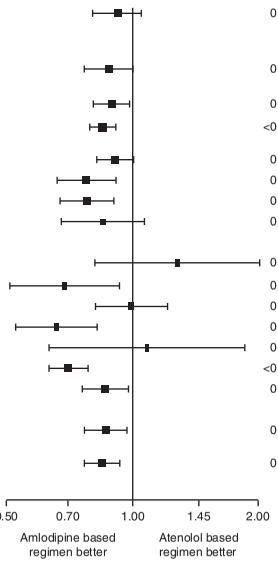


Figure 6.13. Effect of treatment (amlodipine-based regimen vs. atenolol-based regimen) on all end points in the ASCOT-BPLA study. Rates are per 1000 patient years.

Reprinted from Dahlof B, Sever PS, Poulter NR, 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 with permission from Elsevier.

by minimizing or eliminating the metabolic and heart rate adverse events seen with the first-generation beta-blockers. Both carvedilol and nebivolol have neutral glycemic and lipid parameters[198,205] and could therefore become the preferred beta-blockers for patients with CKD, many of whom have diabetes, obesity, and/or dyslipidemia.

Carvedilol, a beta-1, beta-2, and alpha-1 adrenoreceptor antagonist, has demonstrated multiple hemodynamic, anti-ischemic, and antioxidant properties,[206–208] emerging as a unique member of the beta-blocker class that could be particularly beneficial for CKD patients. The Glycemic Effects in Diabetes Mellitus Carvedilol-Metoprolol Comparison in Hypertensives trial examined the effects of different beta-blockers on changes in albuminuria in the presence of RAAS blockade.[209] Participants with hypertension and type 2 diabetes were randomized to either metoprolol (n = 737) or carvedilol (n = 498) taken in addition to ACE inhibitors or ARBs. Of these subjects, about 75% had valid urine albumin:creatinine measurements at baseline and after 5 months of treatment. A 14.0% reduction in albuminuria was observed with carvedilol while albuminuria slightly increased with metoprolol (**Figure 6.14**); of those with normoalbuminuria

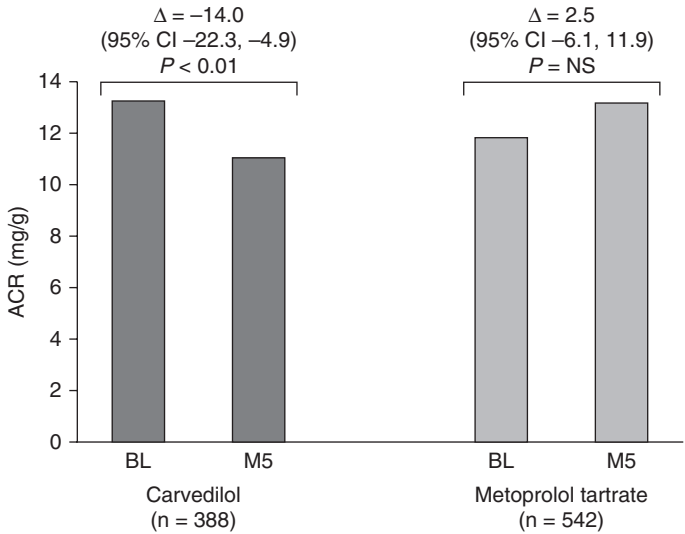


Figure 6.14. Individual treatment group changes in urine albumin-to-creatinine ratio from baseline (BL) to maintenance month 5 (M5) for each treatment group in the GEMINI study.

Reprinted from Bakris GL, Fonseca V, Katholi RE, et al. Differential effects of beta-blockers on albuminuria in patients with type 2 diabetes. *Hypertension*. 2005;46(6):1309–1315 with permission fron the American Heart Association.

at baseline, significantly fewer progressed to microalbuminuria on carvedilol (6.6%) versus metoprolol (11.1%). This differential effect on urinary albumin excretion was not related to differences in blood pressure or achievement of blood pressure goal, outcomes which were virtually equal in both groups. Instead, presence of metabolic syndrome at baseline was the only independent predictor of worsening albuminuria throughout the study ($P = 0.004$).

Nebivolol induces endothelium-dependent vasodilation by stimulating nitric oxide bioactivity.[205,208] In a small study of 40 subjects with untreated hypertension (mean blood pressure 160/98 mm Hg) randomized to atenolol or nebivolol for 4 weeks, both beta-blockers produced an equal reduction in brachial blood pressure, but aortic pulse pressure was reduced to a greater extent by nebivolol. Pulse wave velocity was decreased significantly by both therapies, but only nebivolol significantly reduced augmentation index and pulse pressure amplification, all surrogate measures of vascular stiffness (**Figure 6.15**).[210] The authors

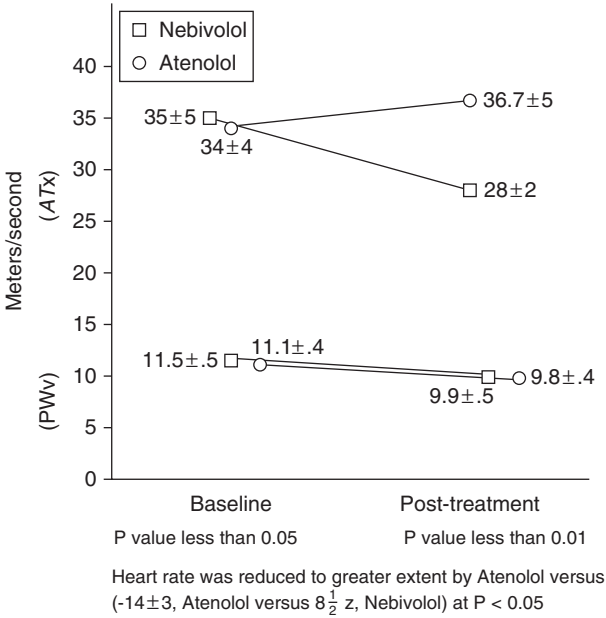


Figure 6.15. Changes in measures of vascular stiffness—augmentation index and pulse wave velocity—after 4 weeks of treatment with atenolol, 50 mg/day, or nebivolol, 5 mg/day.

Adpated from Mahmud A, Feely J. Beta-blockers reduce aortic stiffness in hypertension but nebivolol, not atenolol, reduces wave reflection. *Am J Hypertens.* 2008;21(6):663–667.

concluded that nebivolol, in contrast to atenolol, has an effect on small muscular arteries due to increased levels of nitric oxide, a property that may impart important and distinct hemodynamic effects for this new drug that could translate to improved outcomes, including renal outcomes. To date, however, renal outcome studies with this agent do not exist. A prospective, open-label, multicenter, postmarketing surveillance study of nebivolol was conducted in 2838 patients with hypertension and type 2 diabetes given nebivolol, either as monotherapy or as add-on therapy to other antihypertensive agents, over a minimum period of 3 months. As mean blood pressure decreased from 156/92 mm Hg to 135/81 mm Hg during the treatment period, this reduction of BP was associated with improvements in most metabolic parameters, including lipid levels, glycosylated hemoglobin (HbA1c), and microalbuminuria.[211]

Other Antihypertensive Agents

As impaired kidney function often is associated with difficult-to-control blood pressure, clinicians are often compelled to prescribe 3 or more agents to hypertensive patients with CKD. As noted earlier, spironolactone has emerged as an excellent add-on therapy for this type of resistant hypertension,[146,147] but the risk for severe hyperkalemia can preclude its use in CKD patients. Therefore, other antihypertensive agents are used to treat elevated blood pressures in CKD patients not responding to initial therapies. These agents are older, generic, and inexpensive, yet they are also frequently associated with adverse events.

Both centrally acting alpha agonists (e.g., clonidine, methyldopa) and selective alpha-1 blockers (e.g., doxazosin, terazosin) have strong, often rapid effects on blood pressure. In addition, these alpha-adrenergic agents have beneficial effects on lipid metabolism (increasing HDL and decreasing LDL cholesterol levels) and can improve insulin sensitivity. However, due to their relatively high incidence of side effects—including dry mouth, sedation, weakness, syncope, sexual dysfunction, and rebound hypertension after withdrawal of therapy—these agents are not recommended for use as first- or even second-line therapy.[2] Dizziness and syncope may be minimized by starting with a low dose of a long-acting agent (e.g., doxazosin) administered at bedtime,[212] and the selective alpha-1 blockers have shown some benefit in older men with symptomatic benign prostatic hyperplasia. Still, the observation in ALLHAT that doxazosin, compared to chlorthalidone, significantly increased the risk of developing congestive heart failure has substantially limited use of this drug.[213]

Hydralazine and minoxidil are potent peripheral vasodilators that can be used, in severe cases, to lower blood pressure.[214] These drugs, however, can also cause lower extremity edema, tachycardia, and (rarely) pleural or pericardial effusions. Therefore, when used, they are almost always prescribed alongside a beta-blocker and loop diuretic in order to minimize these side effects. The incidence of adverse events and, in particular, pericardial effusion is higher in CKD patients than in patients with normal renal function.[215–217] As with the alpha-acting agents, the peripheral vasodilators are not recommended for routine use and are typically reserved for patients whose blood pressures remain elevated despite use of 3 or more drugs.

Fixed-Dose Combination Agents and Newer Agents "In the Wings"

New agents to treat blood pressure are continuously under development and testing. In some instances, these new medications are upgrades within an already well-established class of antihypertensives. A new angiotensin receptor blocker (ARB), azilsartan medoxomil, is currently being tested in phase III clinical trials. This may not be just another ARB: in early head-to-head

comparisons, azilsartan demonstrated better anti-hypertensive effects than other ARBs. Whether this will translate into additional clinical benefit remains to be seen.

We expect greater use of combination therapies in the future (**Table 6.5**), strengthened by a 2010 position paper from the American Society of Hypertension that recommended routine initiation of combination therapy in patients who will require >20/10 mm Hg blood pressure reduction to achieve goal blood pressure targets. The paper critically reviewed combination agents and placed them into categories of what is effective for blood pressure lowering in the context of outcomes. While the RAAS blockers with diuretics are very effective agents, RAAS blockers combined with calcium channel blockers may provide greater benefit to older patients at high cardiovascular risk as evidenced by the results of the ACCOMPLISH trial.[188] There are three RAAS/CCB combinations; amlodipine/benazepril is generic in the 5/20 mg/day dose, while amlodipine/valsartan and amlodipine/olmesartan are not generic but available in multiple dose combinations.

Recently arrived and on the horizon are triple drug combinations that include amlodipine with either valsartan or olmesartan combined with hydrochlorothiazide. The triple combination with valsartan is now available, and the combination with olmersartan will soon be available, too. Other combinations using angiotensin receptor blockers with neutral endopeptidase inhibitors are on the horizon and may offer greater efficacy for BP lowering in certain situations.

Table 6.5. Drug Combinations in Hypertension: Recommendations

Preferred
ACE inhibitors/diuretic*
ARB/diuretic*
ACE inhibitor/CCB*
ARB/CCB*
Acceptable
β-blocker/diuretic*
CCB (dihydropyridine)/β-blocker
CCB/diuretic
Renin inhibitor/diuretic*
Renin inhibitor/ARB*
Thiazide diuretics/K+ sparing diuretics*
Less effective
ACE inhibitor/ARB
ACE inhibitor/β-blocker
ARB/β-blocker
CCB (nondihydropyridine)/β-blocker
Centrally acting agent/β-blocker

ARB, angiotensin receptor blocker; ACE, angiotensin-converting enzyme; CCB, calcium channel blocker.

*Single pill combinations available in the United States.

Source: Gradman AH, Basile JN, Carter BL, Bakris GL. Combination therapy in hypertension. *J Am Soc Hypertens*. 2010;4(2):90–98.

No less important, and potentially more exciting, are entirely new classes of anti-hypertensive therapies currently under investigation. Aldosterone synthase inhibitors have been studied as alternatives, and possible improvements, upon mineralocorticoid receptor blockers,[218] driven by the hypothesis that aldosterone may exert some of its effects via non-mineralocorticoid receptors. Endothelin antagonists, mentioned briefly in chapter 5, have shown short-term efficacy in reducing blood pressure and proteinuria in patients with CKD, yet recent reports on an increased risk of fluid overload and congestive heart failure with these agents[219] highlight the importance of waiting for longer-term data when evaluating new agents.

For years, investigators have sought out a vaccine as a possible strategy to prevent development or progression of hypertension. The most recent example is the use of modified angiotensins as immunogens to induce blockade of the RAAS. This vaccine strategy has been explored as an alternative to conventional RAAS-blocking oral therapies. At least two angiotensin-based vaccines are currently in development; in phase II studies in hypertensive patients, the vaccines have demonstrated limited efficacy compared to existing RAAS-blocking drugs.

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Chapter 7

Controversies in Hypertension and Chronic Kidney Disease

Although hypertension is widely recognized as a major determinant of kidney and cardiovascular disease risk, a number of issues in the characterization and management of hypertension remain incompletely understood. These controversial subjects continue to fuel research studies—from large-scale clinical trials to epidemiologic investigations to basic, animal-model research—and inspire impassioned editorials from leading clinician-scientists.

DUAL BLOCKADE OF THE RENIN ANGIOTENSIN ALDOSTERONE SYSTEM

Blockade of the renin angiotensin aldosterone system (RAAS) lowers blood pressure, decreases morbidity and mortality in patients with congestive heart failure (CHF), and slows the rate of glomerular filtration rate (GFR) decline in patients with chronic kidney disease (CKD) stages 3–5.[1–5] However, significant numbers of patients with chronic heart and kidney disease continue to progress at a higher than predicted rate despite this standard therapy; for example, current treatment regimens that include an angiotensin-converting enzyme (ACE) inhibitor or angiotensin-II receptor blocker (ARB) have not been proven to halt kidney disease progression in most adult patients over the long term.[2,6,7] Incomplete blockade of the RAAS at recommended doses may be one explanation for this observation.[8,9]

One option to counter this potentially incomplete RAAS blockade is to use higher—sometimes referred to as "ultrahigh"—doses of ACE inhibitors or ARBs that in small, short-term clinical studies yield better reductions in surrogate outcomes, such as proteinuria reduction, than conventional doses of these agents.[10–13] Long-term data with hard outcomes are currently lacking, however. Supporters of this ultrahigh therapy contend that the FDA-recommended doses of ACE inhibitors and ARBs used in routine practice are inadequate.[14,15] Only one study of ultrahigh doses of ACE inhibitors and ARBs provides valid CKD end-point data. The Renoprotection of Optimal Antiproteinuric Doses study used a combined primary outcome of doubling of serum creatinine, end stage renal disease, and death. Compared with conventional doses, ultrahigh doses of benazepril and losartan were associated with a 51% ($p = 0.03$) and 53% ($p = 0.02$) reduction, respectively, in the risk for the primary end point.[16]

Another approach is to combine an ACE inhibitor with an ARB. Theoretically, this dual blockade should further suppress the RAAS and, by extension, yield better cardiovascular and kidney outcomes than either agent alone. Combinations of ACE inhibitors and ARBs have generally been shown to produce small but significant additional reductions in proteinuria (approximately 20%) and blood pressure (approximately 2–3 mm Hg) compared with either monotherapy. The effects on harder cardiovascular and kidney outcomes in clinical trials with this combination therapy have thus far been mixed.

In the Randomized Evaluation of Strategies for Left Ventricular Dysfunction pilot study, ACE inhibitor/ARB combination therapy, compared to monotherapy, significantly limited increases in end diastolic and end systolic volumes and reduced brain natriuretic peptide, a biomarker of heart failure.[17] In the Candesartan in Heart Failure: Assessment of Mortality and Morbidity (CHARM–Added) trial, after a median follow-up of 41 months, fewer patients taking the ACE inhibitor/ARB combination (38%), compared with those receiving ACE inhibitor plus placebo (42%), experienced the primary composite end point of cardiovascular death or hospitalization for chronic heart failure ($P = 0.01$).[18]

However, some recent, large trials have failed to find better cardiovascular outcomes with dual RAAS blockade despite better blood pressure reductions and, perhaps more importantly, have reported an increased incidence of adverse events associated with combination therapy. The Valsartan in Acute Myocardial Infarction trial reported similar rates of all-cause mortality, death from cardiovascular events, recurrent myocardial infarction, and hospitalization for heart failure for all 3 of its treatment groups (ACE inhibitor, ARB, and ACE inhibitor/ARB) accompanied by significantly ($P < 0.05$) more adverse events in the combination therapy group.[19] In the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET), combination therapy produced no greater reduction in the risk of the primary end point of death from cardiovascular events, myocardial infarction, stroke, or hospitalization for heart failure, but was associated with an increased risk of hypotension ($P < 0.001$), syncope ($P = 0.03$), hyperkalemia ($P < 0.001$), and acute renal impairment ($P < 0.001$).[20,21]

Studies examining the effects of ACE inhibitor/ARB combinations on the progression of kidney disease have also produced mixed results. Most trials have been small and of short duration, using the surrogate end point of proteinuria, rather than measurements of renal function, as the primary outcome.[22] Two recent meta-analyses of patients with diabetic and nondiabetic proteinuric renal disease found that ACE inhibitor/ARB combination therapy significantly reduces proteinuria to a greater extent than either agent alone,[22,23] yet the decrease in proteinuria observed in ONTARGET during combination therapy did not result in improved kidney outcomes.[24] In this trial, the number of events for the composite primary outcome of death, dialysis, or doubling of serum creatinine was similar for ramipril and telmisartan alone but was significantly higher ($P = 0.04$) in the ramipril/telmisartan combination group. In addition, there was an initial, steeper decline in estimated GFR in the combination group despite significantly lower albuminuria. Unfortunately, the ONTARGET study was not designed as a renal end point trial; in fact, the major differences in renal end points had to do with dialysis treatment for episodes of hyperkalemia and not sustained end stage renal disease, which was not statistically different between dual-therapy and monotherapy groups. Furthermore, doubling of serum creatinine, a surrogate end point, was not confirmed by repeated measurements of creatinine, and the incidence of doubling was not significantly greater in the combination arm.

The results from ONTARGET have sounded an alarm as to whether dual blockade of the RAAS should still be employed for patients with CHF and/or CKD.[25–29] The reasons for the lack of additional benefits with combination therapy despite an additional reduction in systolic blood pressure of 3.4 mm Hg compared with monotherapy are unclear. As the investigators pointed out, the majority of patients were also receiving statins, beta-blockers, and antiplatelet medications so that additional RAAS blockade with the ACE inhibitor/ARB combination may not have had much room to yield additional clinical benefit.[21] In addition, many of the subjects randomized to receive dual therapy were already normotensive and, in regular practice (i.e., outside a research setting), would likely have not been offered dual therapy. With regards to the risk for adverse renal outcomes, to date there are still no long-term, large-scale renal outcomes trials using any RAAS combination therapy as compared with monotherapy in diabetics or nondiabetics. A large-scale Veterans Administration cooperative trial (VA NEPHRON-D Study), now in progress, will compare, among patients with type 2 diabetic nephropathy, an ACE inhibitor/ARB combination and an ACE inhibitor alone using outcomes of progression to later stages of CKD, progression to end stage renal disease, and death.[30]

Table 7.1. Effects of DRIs, ACE-I's, ARBs, and MRBs on components of the renin angiotensin aldosterone system

	DRI	ACE-I	ARB	MRB
Plasma renin activity	↓	↑	↑	↑
Plasma renin concentration	↑	↑	↑	↑
Angiotensin I	↓	↑	↑	↑
Angiotensin II	↓	↓	↑	↑
Aldosterone	↓	↓ or ↑[a]	↓ or ↑[a]	↑

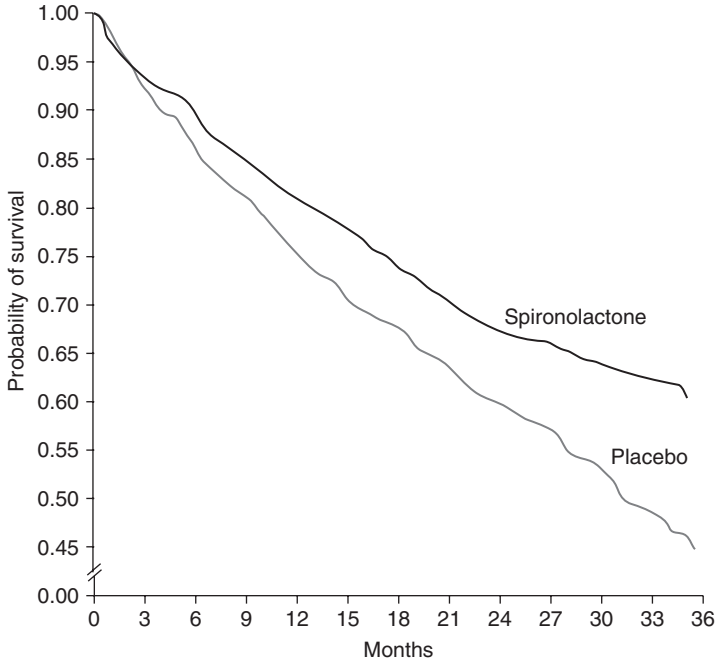
ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; DRI, direct renin inhibitor; MRB, mineralocorticoid receptor blocker.

[a] Aldosterone levels increase from baseline in 30–40% of patients on long-term ACE-I and/or ARB therapy.[37]

Source: Adapted from Bomback AS, Toto R. Dual blockade of the renin-angiotensin-aldosterone system: beyond the ACE inhibitor and angiotensin-II receptor blocker combination. *Am J Hypertens*. 2009;22(10): 1032–1040.

Increased appreciation of the role of aldosterone in the pathogenesis of cardiovascular and kidney disease,[31–33] as well as the recent availability of the direct renin inhibitor, aliskiren,[34] suggest additional combination strategies that offer novel ways to maximally suppress the RAAS.[35] Indeed, inhibition of the RAAS at various points along the cascade can have differential effects on other components of the system, potentially resulting in incomplete blockade (**Table 7.1**). Consequently, it may be more beneficial to combine an ACE inhibitor with an agent that blocks the RAAS more proximally (aliskiren) or distally (spironolactone or eplerenone) than with an ARB. These alternative combination therapies suggest it is too early to proclaim the end of dual blockade of the RAAS as an effective treatment strategy.[36] Perhaps the most important lesson from ONTARGET is that, when evaluating combination therapy, surrogate outcomes such as proteinuria (in CKD trials) and left ventricular mass (in CHF trials) are not sufficient by themselves.

Notably, the best support for using dual RAAS blockade stems from 2 landmark CHF clinical trials that used hard end points of mortality and combined an ACE-I or ARB plus mineralocorticoid receptor blockade (MRB; spironolactone or eplerenone). In the Randomized Aldactone Evaluation Study (RALES),[38] 1663 patients with severe heart failure and a low left ventricular ejection fraction were randomized to receive the MRB spironolactone or placebo on top of conventional CHF therapy, including an ACE inhibitor. The trial was stopped after 24 months owing to a 30% lower risk of death in the group receiving spironolactone ($P < 0.001$) (**Figure 7.1**). Similar results were observed in the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS),[39] a larger trial of 6642 patients with left ventricular systolic dysfunction and heart failure after myocardial infarction, who were treated with eplerenone, a selective aldosterone blocker. Approximately 90% of these subjects were already taking an ACE inhibitor or ARB. Compared with placebo, eplerenone significantly reduced deaths from any cause ($P = 0.008$) and deaths from cardiovascular events or hospitalizations for cardiovascular events ($P = 0.002$).



No. at risk

Placebo	841	775	723	678	628	592	565	483	379	280	179	92	36
Spironolactone	822	766	739	698	669	639	608	526	419	316	193	122	43

Figure 7.1. Kaplan-Meier analysis of the probability of survival among patients randomized to placebo or spironolactone in the RALES trial.

Adapted from Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. *N Engl J Med*. 1999;341(10):709–717.

A number of small, short-term, clinical studies have examined the effects of adding spironolactone or eplerenone to ACE inhibitor and/or ARB therapy in patients with proteinuric kidney disease, typically patients with diabetic nephropathy.[40–49] These studies have consistently shown that adding MRB therapy reduces proteinuria in patients on long-term ACE inhibitor or ARB therapy with persistent proteinuria. In a systematic review of 15 studies of 436 patients with proteinuric kidney disease, ranging from randomized, controlled trials to case reports, the addition of an MRB to ACE inhibitor and/or ARB therapy resulted in a

15–54% reduction in proteinuria from baseline.[50] While these promising data, together with the results of RALES and EPHESUS, suggest that the addition of an MRB to an ACE inhibitor or ARB may be an effective treatment strategy in CKD for patients who do not fully respond to an ACE inhibitor and/or ARB, the kidney data still rely on proteinuria as a surrogate outcome and offer no definitive evidence that dual RAAS blockade with MRBs confers long-term renal protection. In addition, MRB-based combination therapy has not been studied in nonproteinuric kidney disease. Finally, the potential adverse effects of MRB therapy on serum potassium levels must also be considered. The overall incidence of clinically significant hyperkalemia in the renal studies of MRB therapy has been low,[50,51] but the subjects in these studies have generally had preserved kidney function (e.g., eGFR $>$ 50 ml/min/1.73 m^2) and low baseline serum potassium levels. In patients with compromised kidney function who are already at risk for hyperkalemia and are already receiving ACE inhibitor or ARB therapy, the risk for hyperkalemia may be disproportionately high.[52]

A growing body of literature also suggests that aliskiren, a direct renin inhibitor (DRI), plus either an ACE inhibitor or an ARB may provide cardiorenal benefits that extend beyond those solely attributable to lowering of blood pressure. In the Aliskiren Observation of Heart Failure Treatment study,[53] 302 subjects were randomized to receive aliskiren (150 mg daily) or placebo for 3 months in addition to standard therapy, which included an ACE inhibitor or ARB. N-terminal prohormone brain natriuretic peptide, an important biomarker of heart failure prognosis and the primary efficacy outcome measure, increased with placebo but decreased with aliskiren ($P = 0.01$) (**Figure 7.2**). Serum levels of the related biomarker brain natriuretic peptide decreased with both placebo and aliskiren, although to a significantly greater extent with aliskiren than with placebo ($P = 0.02$). Aliskiren also caused a greater reduction in plasma renin activity and 24-hour urinary aldosterone excretion compared with placebo. However, results from a study of aliskiren (300 mg), losartan (100 mg), or their combination on left ventricular mass in patients with hypertension and left ventricular hypertrophy did not suggest any additional benefit from dual RAAS blockade in a similar patient population.[54] After 9 months of treatment, left ventricular mass index was significantly reduced in all treatments groups (5.4%, 4.7%, and 6.4% in the aliskiren, losartan, and the combination group, respectively), but combination therapy did not produce any additional benefits.

The Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) trial evaluated the effects of dual blockade of the RAAS with aliskiren and losartan in patients (N = 599) with hypertension and type 2 diabetic nephropathy.[55] Patients were maintained on losartan (100 mg daily) for the duration of the study and were randomized to receive a 6-month treatment with aliskiren or placebo. After 3 months of treatment with aliskiren (150 mg daily), the urinary albumin-to-creatinine ratio had decreased by 11% compared with placebo ($P = 0.02$ vs. placebo) (**Figure 7.3**). Increasing the dose of aliskiren to 300 mg/d caused a further decrease in the urinary albumin to creatinine ratio to 20% ($P < 0.001$ vs. placebo) at study end point (6 months). This reduction in proteinuria occurred in the presence of a small but nonsignificant decrease in blood pressure, suggesting that addition of aliskiren to losartan in this diabetic population had potential renoprotective effects independent of blood pressure. There was no difference in the rates of adverse events or discontinuation rates between the 2 groups. Hyperkalemia was reported in 5.0% of the patients in the aliskiren group and 5.7% in the placebo group. Serum creatinine of $>$2.0 mg/dl (not a primary outcome) occurred in 12.4% of the patients in the aliskiren group and 18.2% in the placebo group.

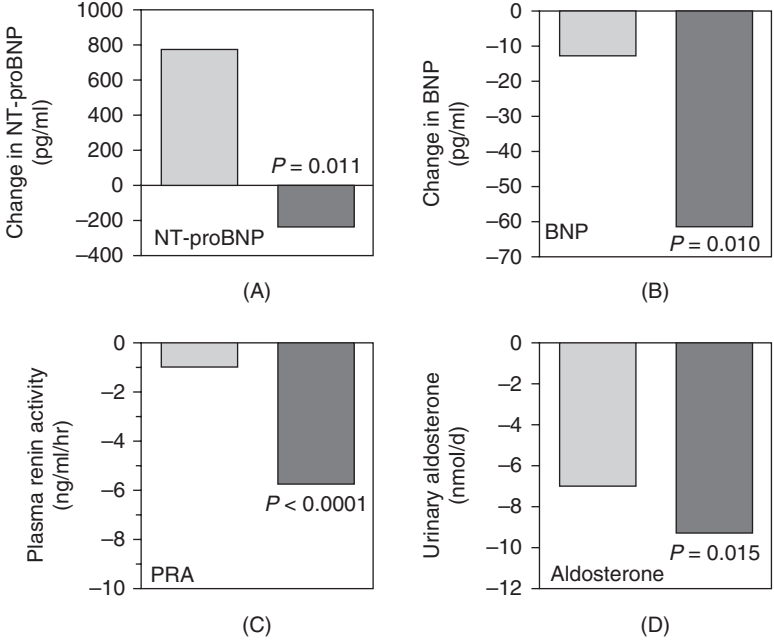


Figure 7.2. Effect of aliskiren on (A) N-terminal proBNP, (B) BNP, (C) plasma renin activity, and (D) urinary aldosterone in patients with chronic symptomatic heart failure. Patients received aliskiren (150 mg/d) (filled bars) or placebo (open bars) in addition to standard therapy with an ACE inhibitor or ARB.

Data from McMurray JJ, Pitt B, Latini R, et al. Effects of the oral direct renin inhibitor aliskiren in patients with symptomatic heart failure. *Circ Heart Fail*. 2008;1(1):17–24.

Like the majority of the studies of dual blockade with the ACE inhibitor/ARB combination, the literature to date on aliskiren-based dual blockade of the RAAS relies on surrogate outcomes such as natriuretic peptide levels and left ventricular mass index (for chronic heart failure) and proteinuria (for CKD). The DRI approach to RAAS suppression is still very recent, and its relatively unblemished record may simply be due to fewer studies, less available data, and overall shorter experience with the agent. Larger, long-term trials with hard, clinically meaningful outcomes such as mortality and progression to end-stage kidney disease are needed to confirm the beneficial effects of dual RAAS blockade with aliskiren. Such trials are under way, using end points of cardiorenal morbidity and mortality in a variety of patient populations,

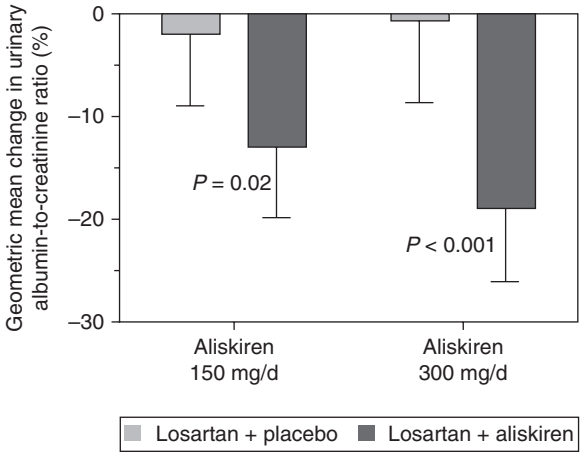


Figure 7.3. Effect of aliskiren combined with losartan on the urinary albumin-to-creatinine ratio in patients with type 2 diabetes and nephropathy. Patients received losartan (100 mg/d) throughout the study and were randomized to receive placebo or 150 mg/d of aliskiren for 3 months followed by 300 mg/d for an additional 3 months.

Data from 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):2433–2446.

including high-risk type 2 diabetes (Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Disease Endpoints)[56] and congestive heart failure (Aliskiren Trial to Mediate Outcomes Prevention in Heart Failure).[57]

TARGET BLOOD PRESSURE IN ABSENCE OF ALBUMINURIA

The *Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure* (*JNC 7*), published in 2003,[58] included a separate recommendation for patients with CKD, defined by either reduced GFR or presence of albuminuria (>300 mg/day on 24-hour urine collection or >200 mg albumin/g creatinine on spot morning urine collection). For these patients, the recommended goal blood pressure target is <130/80 mm Hg, lower than the recommended blood pressure in uncomplicated hypertension. The same blood pressure goal of <130/80 mm Hg was also recommended for patients with diabetes, with or without concomitant kidney disease. The *Eighth Report of the Joint National*

Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (*JNC 8*), projected for release in 2010, is expected to recommend the same goal blood pressure for patients with CKD.

All current blood pressure guidelines—including those issued by the American Heart Association,[59] the World Health Organization (WHO) and the International Society of Hypertension,[60] and the ESH/ESC,[61] in addition to *JNC 7*—emphasize that patients' overall cardiovascular risk should be the basis upon which to decide whether to initiate pharmacologic therapy and to what treatment goal. However, there are differences among panels in terms of which patient groups warrant more aggressive treatment goals. Because patients with CKD are more likely to die of cardiovascular disease than to progress to end stage renal disease, most treatment guidelines consider CKD to be a coronary artery disease equivalent that requires more aggressive therapy. Still, there is considerable debate as to whether reduced GFR without abnormal urinary albumin excretion poses the same risk as reduced GFR with albuminuria, and therefore treatment goals for these distinct patient populations need not necessarily be the same.

Abnormal urinary albumin excretion, most often found in patients with diabetes, is one of the earliest signs of abnormal vascular responsiveness and evidence for vascular inflammation. Microalbuminuria (albumin excretion of 30–300 mg/day) is a marker of endothelial dysfunction and an independent risk factor for cardiovascular events.[62–64] Repeated elevations of the urine albumin concentration in the microalbuminuria range suggest but do not definitively indicate kidney disease, as increased urinary albumin excretion may solely reflect generalized endothelial dysfunction.[65–69] Macroalbuminuria or overt proteinuria (albumin excretion greater than 300 mg/day) is associated with a much higher cardiovascular risk and clearly indicates presence of kidney disease.[70] A direct relationship exists between the degree of proteinuria and risk of progression to end stage renal disease.

A reduced eGFR poses an increased cardiovascular risk, in part because it represents a higher prevalence of associated risk factors, such as uncontrolled hypertension and dyslipidemia. Several large studies have shown that patients with a reduced eGFR have higher blood pressure and total cholesterol, lower HDL, and are more likely to have ischemic heart disease, left ventricular hypertrophy, diabetes, and heart failure.[71–73] Consequently, it has been postulated that reduced eGFR may be a marker for more severe vascular disease.[74] A reduced eGFR may also be an independent predictor of an adverse cardiovascular prognosis. Data from the Kaiser Permanente Renal Registry, which followed more than 1 million adults, showed a graded, independent association between eGFR and cardiovascular events. Patients with a GFR of 40–59 ml/min experienced a 40% increase in events compared to those with normal renal function, which rose to a 100% increase for 30–44 ml/min, and a 340% increase for less than 15 ml/min.[75]

While evidence supports the assertion that abnormal urinary albumin excretion and reduced GFR pose additional risk, the evidence supporting lower blood pressure goals for these conditions is relatively weak. Prospective clinical trial data generally support the notion that lower is better in terms of reducing cardiovascular events, but this has typically meant lower than a control group above a diastolic blood pressure of 80 mm Hg rather than blood pressure lower than the current guideline values. For example, the Hypertension Optimal Treatment study showed that diabetics in the lowest target group (those with a diastolic blood pressure $<$80 mm Hg) had a 51% reduction in major cardiovascular events compared

to the group with a goal of <90 mm Hg.[76] However, in this trial, there was very little separation between blood pressure groups, and no group achieved a mean diastolic pressure below 80 mm Hg. Indeed, few of the large hypertension clinical studies actually reached a mean BP of <130/80 mm Hg; among 10 major trials, the mean systolic blood pressure ranged from 132 to 151 mm Hg.[76–85]

Thus, much of the data behind the goal of <130/80 mm Hg come from epidemiologic studies and post hoc analyses of randomized clinical trials. For example, in the Prospective Studies Collaboration, which followed more than 900,000 patients, an increase in mortality from ischemic heart disease or stroke was already seen with blood pressures in the range of 135/85 mm Hg, when compared to 115/75 mm Hg.[86] In the Irbesartan Diabetic Nephropathy Trial, progressively lower achieved systolic pressure to 120 mm Hg predicted a decline in cardiovascular mortality and CHF episodes, but a systolic pressure below this threshold was associated with an increase in cardiovascular mortality and CHF events.[87] In the International Verapamil-SR Trandolapril trial, the subgroup with a mean blood pressure of 125/75 experienced a 28% reduction in events compared to the patients with a mean BP of 142/80.[88] However, a recent Cochrane Collaboration review, using data from 7 trials with over 22,000 subjects, concluded that targeting a blood pressure below 140/90 mm Hg did not prolong survival or reduce stroke, heart attack, heart failure, or kidney failure; subgroup analyses of subjects with diabetes and/or CKD did not find evidence for lower target pressures in these patient populations, either.[89]

Indeed, for kidney disease outcomes, all trials that randomized to different blood pressure levels failed to show that lower goal blood pressure slowed progression of kidney disease except in patients with both severely reduced eGFR (<40 ml/min/1.73 m^2) and proteinuria above 1 g/day.[69] Post hoc analyses of 3 CKD outcomes trials—the Irbesartan in Diabetic Nephropathy Trial,[90] the Reduction of Endpoints in Non-insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) trial,[91] and the African American Study of Kidney Disease and Hypertension (AASK) trial[92]—have demonstrated that a reduction in proteinuria delays progression of kidney disease, but this effect was found to be independent of blood pressure. For diabetics (with or without CKD), the Action to Control Cardiovascular Risk in Diabetes trial, recently completed but not yet fully reported, will address whether a lower level of blood pressure is needed to reduce cardiovascular risk. Already, the reported results from this trial on target hemoglobin A1c levels have suggested that a lower-is-better strategy for glycemic control did not reduce major cardiovascular events and increased mortality.[93]

Presently, with the bulk of the evidence for lower blood pressure targets coming from post hoc analyses of clinical trials or epidemiologic, cross-sectional studies, it may be more prudent to *aim* for a blood pressure target of 130/80 rather than to use potentially overaggressive regimens to achieve such targets. This may be particularly true for patients with reduced eGFR without overt proteinuria. The ONTARGET trial, discussed in detail previously, is perhaps the strongest evidence against overtreating blood pressure in this patient population. The subjects in this trial generally had low levels of urinary albumin excretion, and aggressive blood pressure regimens led to excessively high rates of hypotension, syncope, and acute renal impairment with no greater reduction in cardiovascular morbidity or mortality.[20,21]

CHRONOTHERAPY FOR HYPERTENSION

Many, if not all, specific human physiological functions are under the control of a circadian timing system. This includes kidney function and, by extension, the control of blood pressure. The most obvious example of circadian rhythmicity of renal function is the well-recognized difference in urine volume formation and excretion between daytime and nighttime. The urinary excretion of all major solutes—including sodium—also follows a circadian pattern; when this pattern is impaired, disease may ensue. For example, an abnormal circadian rhythm for renal sodium reabsorption is considered one of the major factors leading to the loss of nocturnal blood pressure dipping, which is characteristic for about 1 in 3 hypertensive patients,[94,95] and a surge in blood pressure in the morning hours may be related to worse cardiovascular outcomes.[96]

Chronotherapeutics is the deliberate timing of medications to match their serum and tissue concentrations with known circadian rhythms of disease processes. Because blood pressure can display a relatively predictable circadian variation—including the expected nighttime dip and the accelerated morning rise in pressure—a new field of chronotherapy for hypertension has emerged. The efficacy of chronotherapy relies not only on circadian patterns in physiologic control of blood pressure but also significant administration-time differences in the kinetics (chronokinetics) and the benefits versus adverse effects profiles (chronodynamics) of antihypertensive medications.[97–99]

Hermida's group in Vigo, Spain, has spearheaded the movement toward using chronotherapy in all stages of hypertension. In uncomplicated hypertension, their research has shown that bedtime, as opposed to morning, dosing of various classes of antihypertensive medications leads to improvements in some key blood pressure parameters. For example, in a study of 215 patients with hypertension randomly assigned to receive telmisartan (80 mg daily) as a monotherapy either on awakening or at bedtime, bedtime and morning administration produced similar 24-hour blood pressure profiles, but bedtime administration was more efficient than morning dosing in reducing the mean nocturnal blood pressure. Overall, the number of patients with a nondipper blood pressure pattern at baseline was unaltered in those taking telmisartan on awakening, while nondipping was significantly reduced from 34% to 8% when the same dose was ingested at bedtime.[100] Similar effects have been shown with other ARBs,[101] ACE inhibitors,[102] calcium channel blockers,[103] and alpha-blockers.[104]

While theoretically it may seem simple to change the timing of a blood pressure medication from morning to evening administration, such an adjustment for patients on multiple medications may not be so straightforward. Despite the promising results from the studies done by Hermida's group and other well-recognized hypertension clinical scientists, the evidence thus far is not compelling enough to argue for a shift to a chronotherapeutic regimen for patients with uncomplicated, well-controlled hypertension.

The field of chronotherapy for hypertension, however, may have found its particular niche in the management of patients with resistant hypertension, defined in Chapter 4 as a blood pressure of at least 140/90 mm Hg (or at least 130/80 mm Hg in patients with diabetes or CKD) despite adherence to treatment with full doses of at least 3 antihypertensive medications,

including a diuretic. Most current therapeutic strategies for resistant or refractory hypertension involve adding another drug or changing drug classes for potentially improved synergistic combinations. A recent study, also done by Hermida's group, introduces chronotherapy as an alternative treatment strategy.[105]

Two hundred fifty hypertensive patients receiving 3 antihypertensive drugs in a single morning dose were randomly assigned to 2 groups. Those assigned to the first group had 1 of their drugs changed but kept taking all 3 drugs in the morning; those assigned to the second group had a similar, 1-drug change to their regimen but took this new drug at bedtime. After 12 weeks of therapy, there was no effect on ambulatory blood pressure when all of the drugs were taken on awakening, and the prevalence of nondipping hypertension in this group actually increased during the study period from 79.2% to 86.4%. Conversely, the ambulatory blood pressure reduction in those randomized to 1 drug at bedtime was 9.4/6.0 mm Hg ($p < 0.001$), with the nondipping prevalence dropping from 84.0% to 43.2% during the study period (**Figure 7.4**). Based on this study, a reasonable first step in treating resistant hypertension is to switch at least 1 medication to nighttime dosing.

Minutolo and others examined whether shifting 1 antihypertensive drug from morning to evening restores the circadian rhythm of blood pressure in nondipper patients with CKD.[106] In an uncontrolled, 8-week clinical trial, 32 patients with CKD (mean eGFR 46 ml/min/1.73 m^2) had 1 antihypertensive drug shifted from morning to evening. After the drug shift, the night:day ratio of mean ABP decreased in 93.7% of patients, with normal circadian rhythm restored in 87.5%. Urinary protein excretion decreased as well, from 235 $\pm$ 259 to 167 $\pm$ 206 mg/day ($p < 0.001$). Thus, chronotherapy may prove beneficial for CKD patients with resistant hypertension or nondipping hypertension, again via the simple maneuver of changing 1 antihypertensive medication to nighttime dosing.

GENETICS

The last decade has seen increasingly successful efforts to understand the genetic basis of common human diseases, including type 2 diabetes, coronary artery disease, dyslipidemias, breast cancer, and prostate cancer.[107] To date, however, the search for genetic susceptibility to the common form of hypertension, so-called essential or primary hypertension, has yielded mostly weak and inconsistent evidence.[108] As discussed at the beginning of Chapter 4, advances in our understanding of genetics could someday allow physicians to identify the cause(s) of hypertension for all patients, thus obviating the terms *primary* and *essential* hypertension.

Early studies on the genetic susceptibility to essential hypertension suggested that large changes in a few genes could be responsible for this worldwide problem. Lifton and colleagues helped identify mutations in at least 10 genes shown to alter blood pressure; most of these were rare mutations imparting large, quantitative effects that either raised or lowered blood pressure by affecting salt and water reabsorption in the kidney.[109–115] However, subsequent genome-wide association studies on large-scale population samples, such as the Wellcome Trust Case Control Consortium[116] and Diabetes Genetics Initiative,[117] did not find any genetic variant (or variants) significantly associated with hypertension and/or blood pressure traits.

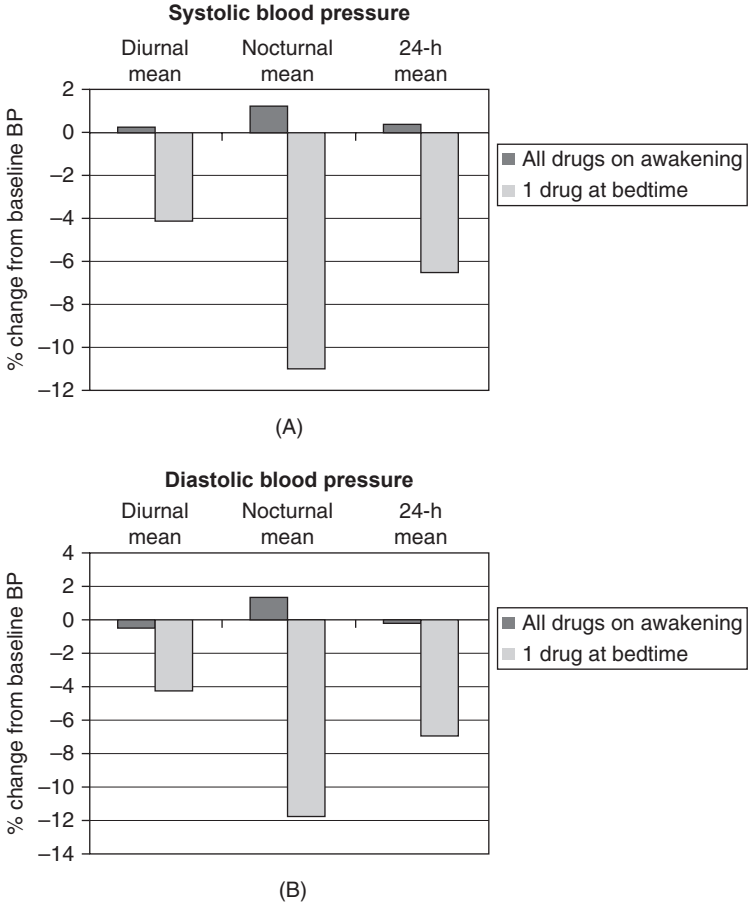


Figure 7.4. Ambulatory (A) systolic and (B) diastolic blood pressure changes during a 12-week study of chronotherapy in resistant hypertension. Changing 1 of 3 medications only led to significant blood pressure reductions if the new medication was taken at bedtime. The biggest effect of chronotherapy was on nocturnal mean blood pressure.

Data from Hermida RC, Ayala DE, Fernandez JR, Calvo C. Chronotherapy improves blood pressure control and reverts the nondipper pattern in patients with resistant hypertension. *Hypertension*. 2008;51(1):69–76.

A more recent genome-wide association study on over 1000 African Americans—a minority group marked by more frequent and more severe hypertension than other population subgroups in America—found evidence to suggest that genetic variants in 5 genes are significantly associated with systolic blood pressure levels; the evidence for genetic variants influencing diastolic blood pressure levels was weaker. Two of these genes, SLC24A4 (a sodium/potassium/calcium exchanger) and CACNA1H (a voltage-dependent calcium channel) are potential candidate genes for blood pressure regulation, and the latter is a drug target for a class of calcium channel blockers.[118]

Overall, however, an increasing body of data indicates that multiple, small, independent changes in many genes—rather than large, predictable changes in a few genes—underlie the genetic susceptibility to essential hypertension.[119–121] Even the relatively successful genome-wide association studies, such as the one cited previously and other recent reports by Levy and colleagues[122] and Newton-Cheh and colleagues,[123] tend to identify dozens of candidate genes. With so many candidate genes, it will likely be difficult to establish a causative link between inherited differences in a human population. Therefore, one approach toward studying the genetics of hypertension is to create differences in a candidate gene in an animal model, a research model that has been used to great success by the Nobel Prize winner Oliver Smithies and his colleagues.[124–127]

An excellent example of this route of investigating and uncovering the genes of human hypertension are the reports on aldosterone synthase gene disruption. An investigation into the genetics of aldosterone production is appropriate as most of the mutations identified in the pathogenesis of hypertension typically translate to how the kidney processes salt and water. Aldosterone synthase (AS) catalyzes the last step of aldosterone synthesis. In humans, a rare, autosomal recessive mutation in the AS gene causes AS deficiency, manifested phenotypically as hyperkalemia, hypotension, metabolic acidosis, and markedly elevated plasma renin activity.[128]

Makhanova and others performed two related series of experiments in mice in which they altered the gene for AS. In the first series, these investigators disrupted the coding region of the mouse AS gene; compared to wild-type ($AS^{+/+}$) and heterozygous ($AS^{+/-}$) mice, the AS-null mice ($AS^{-/-}$) had significantly lower blood pressures on normal-salt and low-salt diets. Interestingly, heterozygous, but not wild-type mice, were able to lower their blood pressures with a low-salt diet (**Figure 7.5**).[129,130] The second series of experiments used mice with a genetically modified increased expression of the AS gene ($AS^{hi/hi}$).[131] Changes in dietary salt did not affect the blood pressure of wild-type mice. In contrast, the $AS^{hi/hi}$ mice had significantly higher mean blood pressure on a high-salt diet than on a low-salt diet and than wild-type mice on either diet (**Figure 7.6**). The $AS^{hi/hi}$ mice also had marked differences in plasma aldosterone levels while on low-, normal-, and high-salt diets, thus reflecting an impaired ability to modulate aldosterone secretion (and hence salt and water reabsorption) in the face of changes in sodium intake (and overall volume status). Taken together, these experiments show that even a mild change in either direction of AS expression makes blood pressure sensitive to salt, suggesting that genetic differences of AS levels in humans may influence how dietary interventions, such as salt content in diet, affect blood pressure control.

Pharmacogenomics describes how genetic variations can influence drug response in patients. Specifically, pharmacogenomic researchers explore whether detectable genetic differences translate to detectable effects of a drug—both beneficial and adverse—on patients. The hope is that pharmacogenomics will allow a rational, informed method to tailor

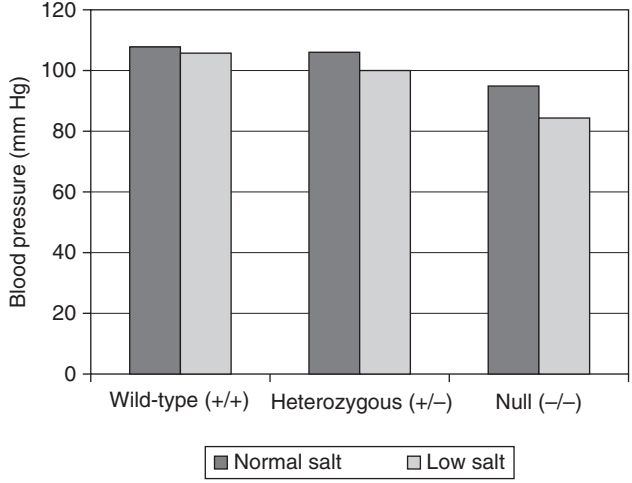


Figure 7.5. Blood pressure variations during normal- and low-salt diets for aldosterone synthase wild-type, heterozygous, and null mice. Although there were no significant differences in blood pressure between wild-type and heterozygous mice on normal salt diet, the mean blood pressure of heterozygous mice on low-salt diet was significantly decreased compared with the unchanged pressure of wild-type mice on low-salt diet.

Adapted from Makhanova N, Sequeira-Lopez ML, Gomez RA, Kim HS, Smithies O. Disturbed homeostasis in sodium-restricted mice heterozygous and homozygous for aldosterone synthase gene disruption. *Hypertension*. 2006;48(6):1151–1159.

drug therapy toward a patient's genotype, thereby maximizing efficacy and minimizing adverse effects. The term *personalized medicine* has been used for such an approach, in which drugs and drug combinations are optimized according to each individual's unique genetic makeup. Much of the pharmacogenomic research into hypertension and CKD has been on patients' response to ACE inhibitors and ARBs, again highlighting the importance of the renin angiotensin system (and its blockade) in the pathogenesis (and treatment) of chronic hypertension and kidney disease. Variations in the angiotensin-converting enzyme (ACE) gene appear to increase the likelihood that treatment with ACE inhibitors and ARBs will yield better responses in blood pressure, proteinuria, and glomerular filtration rate in patients with and without diabetes.[132–134] Conceivably, evaluating the ACE genotype (or other yet-to-be-determined genetic variants) could someday guide choice of antihypertensive therapy in patients with early or late kidney disease, but presently the data supporting such a pharmacogenomic approach are still only hypothesis generating.

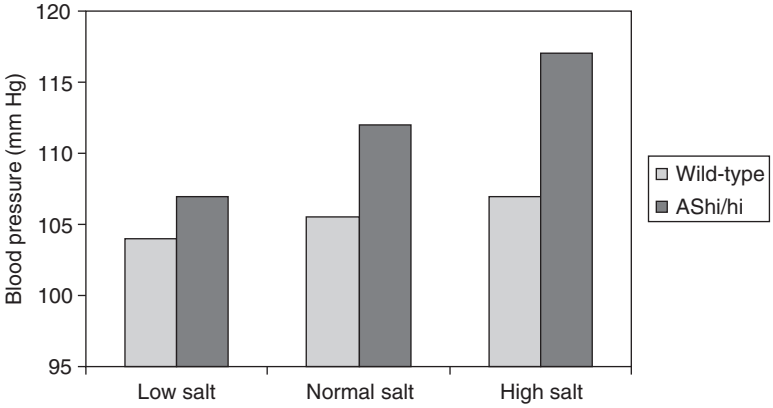


Figure 7.6. Blood pressure variations during low-, normal-, and high-salt diets in wild-type (grey bars) and mice with genetically increased aldosterone synthase expression (black bars, AShi/hi). Altered-salt diets did not significantly affect the blood pressures of wild-type mice but did affect the blood pressures of the AShi/hi mice.

Adapted from Makhanova N, Hagaman J, Kim HS, Smithies O. Salt-sensitive blood pressure in mice with increased expression of aldosterone synthase. *Hypertension*. 2008;51(1):134–140.

Several studies have indicated a genetic component to certain forms of kidney disease. Genes underlying the relatively rare glomerular diseases such as familial forms of focal segmental glomerulosclerosis (FSGS) and membranoproliferative glomerulonephritis have been uncovered, as have the mutations behind more commonly seen entities such as polycystic kidney disease and Alport's syndrome (also known as hereditary nephritis). However, as with essential hypertension, common genetic variants associated with susceptibility to CKD have thus far been difficult to detect. Linkage analyses have suggested candidate genetic locations for susceptibility to albuminuria[135] and glomerular filtration rate[136] among the American Indian population, which bears a disproportionately high rate of kidney disease akin to the disease burden of hypertension among African Americans. Recent genome-wide association studies among participants of four population-based cohorts of European ancestry have identified several mutations associated with susceptibility to kidney dysfunction.[137] One of the genes identified in this study, UMOD, encodes Tamm-Horsfall protein, the most common protein in healthy human urine that, when dysregulated, could also play a role in the pathogenesis of kidney disease.

Perhaps the most exciting discovery in the intersecting fields of the genetics of hypertension and the genetics of kidney disease are the variants in the gene that encodes the molecular motor protein, nonmuscle myosin IIA (MYH9). Variants in MYH9 have been shown in 2 seminal studies, reported back-to-back in *Nature Genetics*,[138,139] to be associated with nondiabetic

kidney disease in African Americans. Kopp and colleagues, studying African Americans with biopsy-proven FSGS (both idiopathic and HIV-associated lesions), reported that a haplotype with the 3 most associated single-nucleotide polymorphisms (SNPs) in intron 23 of MYH9 imparted a 100% attributable risk for HIV-associated FSGS and a 72% attributable risk for idiopathic FSGS. Extension studies revealed that this haplotype among African Americans was significantly associated with nondiabetic forms of end stage renal disease, in particular with clinical (i.e., not biopsy-proven) diagnoses of kidney failure from hypertensive nephrosclerosis.[138] Kao and others, working with DNA samples from 2 large genetic studies, identified multiple common single-nucleotide polymorphisms in the MYH9 gene that were associated with 2–4 times greater risk of nondiabetic ESRD and accounted for a large proportion of the excess risk of ESRD observed in African Americans compared to European Americans.[139]

The studies by Kopp and colleagues and Kao and colleagues highlight the powerful contribution of a single gene to multiple related kidney syndromes; they also show how improved understanding of the pathogenesis of kidney disease can inform physicians and patients as we move into the next era of personalized medicine. Chronic kidney disease in America and the rest of the developed world is predominantly caused by diabetes and hypertension, yet hypertensive nephrosclerosis remains a vaguely defined clinical entity that is often applied to African Americans with hypertension and advanced CKD in the absence of other causes (e.g., diabetes) for renal failure. The markedly lower frequency of the MYH9 risk haplotype in European Americans, compared with African Americans, provides a potential explanation for the observed ethnic differences in the prevalence rates of FSGS and HIV-associated nephropathy, as well as a potential genetic clue as to why African Americans seem to experience hypertension and its harmful effects on the kidney more frequently and more severely.

The MYH9 findings also, again, point to a message that has been stressed throughout this book: hypertension and kidney disease should be viewed along the same disease spectrum. A patient presenting with new-onset hypertension should have his or her kidney function checked, just as any patient with acute or chronic kidney disease should expect his or her physician to explore whether and how antihypertensive therapy should be used. It may, in fact, be true that hypertension causes progressive kidney disease only in genetically susceptible individuals or that it can be the result of a primary, preprogrammed renal disease, as the MYH9 data seem to suggest about the excess risk for kidney failure in African Americans.[140]

Until we identify all of the many genes that surely contribute to the phenotypes of hypertension and chronic kidney disease, we should plug ahead with the essential concepts of diagnosis and management of hypertension and kidney disease discussed in this book. To sum up our message, we paraphrase the well-worn and oft-relied-upon axiom: blood pressure follows the kidney, which, in turn, follows control of blood pressure.

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