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CURRENT AND FUTURE TREATMENT OF HYPERTENSION IN THE SPRINT ERA

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Abstract

Based on the SPRINT trial, it is highly likely that new SPRINT-era guidelines will establish a blood pressure (BP) goal of < 130/80 mm Hg for those aged 50 or older who are at high risk for a cardiovascular event. In this group, SPRINT demonstrated that assignment to an intensive-treatment systolic BP (SBP) goal of < 120 mm Hg significantly reduced cardiovascular events and mortality compared to those assigned to a standard-treatment SPB goal of < 140 mm Hg. This review critically assesses current hypertension guidelines and presents predictions for SPRINT-era guidelines in the elderly, African Americans, and patients with uncomplicated essential hypertension, diabetes, chronic kidney disease, cardiovascular disease, and coronary artery disease. Specific attention is paid to BP goals and preferred pharmacological antihypertensive therapy in these populations, and an algorithm that incorporates the SPRINT trial results is presented. Inhibitors of the renin-angiotensin-aldosterone system as well as calcium channel blockers are universally accepted as first-line therapy in uncomplicated hypertension, but controversy exists over the role of thiazide diuretics and beta blockers. This review also discusses a physiologically and outcomes-based approach to combination therapy for treatment of hypertension.

Introduction

The Systolic Pressure Intervention Trial (SPRINT) was designed to test the hypothesis that treatment to a goal systolic blood pressure (SBP) of < 120 mm Hg (intensive treatment) in patients aged 50 and over at high risk for cardiovascular events (but without diabetes) was superior to an SBP treatment goal of < 140 mm Hg (standard treatment).[1] A total of 9,361 subjects were recruited and randomized, including 3,331 women, 2,648 with chronic kidney disease (CKD), 1,877 with a history of cardiovascular disease, 3,962 minorities, and 2,636 who were aged 75 and older. The primary outcome was a composite of myocardial infarction, acute coronary syndrome not resulting in myocardial infarction, stroke, acute compensated heart failure or death from cardiovascular causes. Over the 3.26 years of follow-up, those randomized to the intensive-treatment arm had a mean SBP of 121.5 mm Hg while those in the standard-treatment had a mean SBP of 134.6 mm Hg. The average medication requirement to achieve these results was 2.8 in the intensive-treatment arm and 1.8 in the standard-treatment arm. Compared to those in the standard-treatment arm, those in the intensive-treatment arm had a 25% lower incidence of the primary outcome ($P < .001$) and 43% lower relative risk of death from cardiovascular causes ($P = .005$).

This remarkable outcome in SPRINT will significantly inform the debate that erupted in 2013 regarding the BP goals and pharmacological treatment for those aged 60 and older with uncomplicated hypertension and in all adults with diabetes, chronic kidney disease (CKD), cardiovascular disease (CVD), and coronary artery disease (CAD). Between 2013 and 2015, multiple guidelines and consensus statements on the treatment of essential hypertension (HTN) were issued from the United States, Europe, Canada, Japan, and international organizations (Table 1).[2-8] Now that the SPRINT results are published, all of these guidelines will certainly be reviewed and new guidelines promulgated in the United States, if not throughout the world. The focus of this review on management of HTN is to critically assess current BP goal guidelines (Table 1) and pharmacological treatment recommendations and, in the context of the SPRINT results, present predictions for SPRINT-era guidelines in the elderly, African Americans, and patients with uncomplicated essential HTN, diabetes, CKD, CVD, and CAD (Figure 1). In addition, first-line antihypertensive and combination therapy recommendations will be reviewed and evaluated in the context of the SPRINT results.

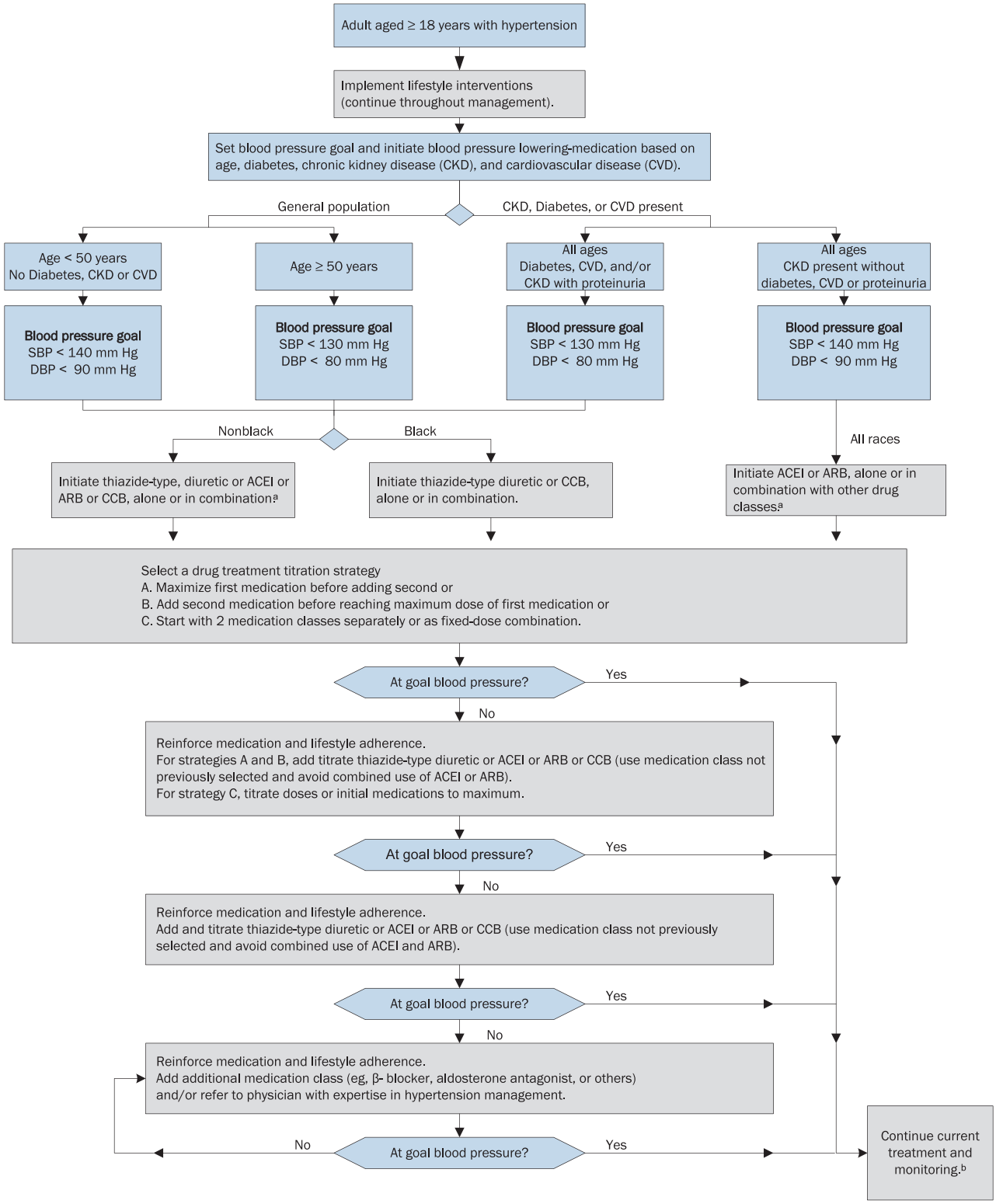
Uncomplicated Hypertension

Based on results of the SPRINT trial, it is highly likely that new guidelines will set a BP goal of < 130/80 mm Hg for all patients aged 50 or older who are at risk for a cardiovascular event (Figure 1). Furthermore, post-SPRINT guidelines will most likely continue to recommend a treatment goal in those under age 50 of < 140/90. This would be consistent with multiple trials conducted in the United States, Great Britain, and Australia in the late 20th century that support a goal in middle-aged adults of < 140/90 mm Hg to prevent stroke and cardiovascular events.[9-11]

Until SPRINT there was virtually no trial-based evidence to support a BP goal of < 130/80 mm Hg in patients aged 60 and older. Prior to SPRINT, no trial in this age group had achieved an average SBP < 143 mm Hg.[12,13] Furthermore, even those individuals who achieved an SBP < 140 mm Hg in these trials did not show incremental benefit. For example, in the Systolic Hypertension in the Elderly Trial (SHEP), where the entry criteria was an SBP > 170 mm Hg, those who achieved an SBP < 160 mm Hg had a 33% reduction in stroke, with a further 5% reduction accrued to those with SBP < 150 mm Hg.[14] However, there was no further reduction in events seen in those who achieved an SBP < 140 mm Hg.

Guideline	Population (s) Addressed in Hypertension Guideline or Statement	Recommended Treatment Goals (mm Hg)		Recommended Blood Pressure Treatment Goals (mm Hg)			Recommended Pharmacological Treatment for Diabetes (mm Hg)	
		Patients < 60 years old	Patients ≥ 60 years old	with type 2 diabetes	with chronic renal failure	elderly patients > 80 years old	without CKD and without proteinuria	with CKD or proteinuria
Author's predictions for 2016 goals based on SPRINT results[1]	All Patients	See Figure 1	See Figure 1	See Figure 1	See Figure 1	See Figure 1	Include ACE or ARB	Include ACE or ARB
ESC/ESH (2013)[2]	All patients	< 140/90	< 140/90	< 140/90	< 140/90	< 150/90	ACE, ARB, thiazide diuretic, CCB, or beta blocker	Include ACE or ARB
JNC-8P (2014)[3]	Uncomplicated HTN, diabetes, CKD, black race	< 140/90	<150/90	< 140/90	< 140/90	< 150/90	Include ACE or ARB	Include ACE or ARB
CHEP (2015)[4]	All patients	< 140/90	<140/90	< 130/80	< 140/90	< 150/90	ACE, ARB, thiazide diuretic, CCB	Include ACE or ARB
ASH/ISH (2014)[5]	All patients	< 140/90	<140/90	< 140/90	< 140/90	< 150/90	Include ACE or ARB	Include ACE or ARB
JSH[6]	All patients	< 140/90	<140/90	< 130/80	< 140/90 and < 130/80 if proteinuria	< 150/90*	ACE or ARB	Include ACE or ARB
AHA/ACC/ASH (2015)[7]	CAD	< 140/90 for CAD, ACS, HF; consider < 130/80 if CAD, post-MI, stoke or TIA, carotid disease, PAD, AAA	< 140/90 for CAD, ACS, HF; consider < 130/80 if CAD, post-MI, stoke or TIA, carotid disease, PAD, AAA	Not stated	Not stated	< 150/90	Not stated	Not stated
ADA (2015)[8]	Diabetes	< 140/90	< 140/90	< 140/90	< 140/90	Not stated	Include ACE or ARB	Include ACE or ARB
*Age > 75								

Table 1. Recommended current blood pressure goals and predictions for future goals in the SPRINT era. AAA: abdominal aortic aneurysm; ACE: angiotensin converting enzyme inhibitor; ACC: American College of Cardiology; ACS: acute coronary syndrome; ADA: American Diabetes Association; ARB: angiotensin converting enzyme inhibitor; ASH: American Society of Hypertension; CAD: coronary artery disease; CHEP: Canadian Hypertension Education Program; CKD: chronic kidney disease; ESC: European Society of Cardiology; ESH: European Society of Hypertension; HF: heart failure; HTN: hypertension; JNC-8P: The Joint National Committee-8 Panel; JSH: Japanese Society of Hypertension; PAD: peripheral vascular disease; SBP: systolic blood pressure; TIA: transient ischemic attack. Adapted from Krakoff LR et al.[16]



SBP indicates systolic blood pressure, DBP, diastolic blood pressure, ACEI, angiotensin-converting enzyme, ARB, angiotensin receptor blocker, and CCB, calcium channel blocker.

[a] ACEI and ARBs should not be used in combination.
[b] If blood pressure fails to be maintained at goal, reenter the algorithm where appropriate based on the current individual therapeutic plan.

Figure 1. Author's predictions for algorithm-based hypertension treatment guidelines in the SPRINT era. Adapted from James PA et al.[3]

As a result, there was debate prior to SPRINT about the BP goal for those between the ages of 60 and 79. This was due to the evidence-based report from the panel members of JNC 8 (hereafter referred to as JNC-8P), who recommended a goal of < 140/90 mm Hg in those under 60 years of age and a more relaxed goal of < 150/90 mm Hg in those aged 60 years and older.[3] The reaction to this recommendation was quite heated. Indeed, almost simultaneously with the publication of the guidelines in

Guideline	ACE/ ARB/CCB	Thiazide Diuretic	β Blocker
ESC/ESH[2]	Yes	Yes	Yes
JNC-8P[3]	Yes	Yes (Chlorthalidone)	No
CHEP (2015)[4]	Yes	Yes	Age < 60
ASH/ISH[5]	Yes	Yes	No
JSH[6]	Yes	Yes	Age < 65
AHA/ACC/ ASH (2015)[7]	Yes	Yes	No
UK NICE[20]	Yes	No	No

Table 2. First-line antihypertensive therapy in uncomplicated hypertension. ACC: American College of Cardiology; ADA: American Diabetes Association; ASH: American Society of Hypertension; CHEP: Canadian Hypertension Education Program; ESC: European Society of Cardiology; ESH: European Society of Hypertension; JNC-8P: The Joint National Committee-8 Panel; JSH: Japanese Society of Hypertension.

early 2014, a minority group of the JNC-8P guidelines writing committee published a critique of the JNC-8P recommendations.[15] Although they agreed there was no hard outcome-based evidence (i.e., stroke, CV disease, or mortality) to support a BP goal of < 140/90 mm in those aged 60 years and older, they argued that relaxation of the guidelines would lead to undertreatment of those groups at high risk for complications of HTN, particularly African Americans. This position was supported by the Association of Black Cardiologists' Board of Directors, who also argued that since no harm could be proven by lowering BP to < 140/90 mm Hg in those aged 60 years and older, it was imprudent to raise the target to < 150/90 mm Hg.[16]

The debate over the past several years regarding treatment goals for those between the ages of 60 and 79 may have diverted attention from the larger issue: Despite decades of efforts and regardless of the goals, hypertension is still undertreated. A recent analysis demonstrated that there are 29.2 million adults in the United States between the ages of 60 and 79 whose SBP is higher than 150 mm Hg.[17] These individuals do not meet BP control levels in any current guideline. Hopefully the SPRINT results will stimulate renewed and reinvigorated efforts to achieve more intensive BP control.

A substudy of SPRINT, called SPRINT-MIND,[18] is hoping to determine if the lower BP goal will better preserve cognitive function. This study is ongoing. The urgency of information regarding cognitive function has been highlighted in a recent report by Mosselli et al., who found that in patients with documented dementia treated with antihypertensive agents, progression of dementia was more rapid in those whose ambulatory daytime SBP was < 128 mm Hg compared to those whose SBP was either between 129 and 144 or > 145 mm Hg.[19] A limitation of this observational study is that it could be subject to confounding and reverse causality, as unidentified factors that lead to progressive dementia may also cause lower BP.

Choice of Antihypertensive Therapy in Uncomplicated HTN: Where is the Debate?

In uncomplicated hypertension, all guidelines recommend either an angiotensin-converting enzyme inhibitor (ACE), an angiotensin receptor blocker (ARB), or a calcium channel blocker (CCB) as first-line therapy (Figure 1, Table 2).[2-8] Virtually all guidelines, with the exception of those from the U.K. National Institute for Health and Care Excellence (NICE),[20] also recommend a thiazide diuretic as a potential first-line therapy. Due to concerns of metabolic disturbances associated with thiazide diuretics (particularly hyperglycemia), in the absence of heart failure, NICE relegates thiazides to second-line therapy for black patients and third line in other ethnic groups. NICE recommends the addition of spironolactone as fourth-line therapy. Since the thiazide diuretic chlorthalidone was a fundamental component of therapy in the SPRINT trial,[18] it is likely that thiazides will remain as first-line therapy in most, if not all, future guidelines.

With the exception of the European Society of Hypertension,[2] virtually no current guideline recommends β blockers as first line in all patients due to concern regarding their relative ineffectiveness compared to other agents in stroke prevention in the elderly and their potential to exacerbate diabetes. Recognizing the pharmacological and possible clinical heterogeneity of β blockers, the European Society of Hypertension has consistently recommended continued use of β blockers as first-line therapy.[2] The Canadian Hypertension Education Program and the Japanese Hypertension Society recommend β blockers in patients under ages 60 and 65, respectively, but recommend other drugs in the elderly or in those with glucose intolerance or diabetes.[4,6] The NICE guidelines have relegated β blockers to fourth-line therapy, except in young patients with "an intolerance or contraindication to ACE inhibitors and angiotensin II antagonists or women of child-bearing potential or people with evidence of increased sympathetic drive."[20]

Combination Therapy

While choice of initial therapy is important, more emphasis needs to be placed on determining the most efficacious drug combination since most patients require at least two drugs for BP control. Combining drugs with different mechanisms of actions is a physiologically based approach associated with more effective BP lowering (Figure 2).[21] The most effective combinations include an ACE or an ARB combined with a CCB or thiazide diuretic, or a β blocker combined with a CCB. Because of the increased incidence of diabetes, the NICE guidelines do not recommend the combination of a thiazide diuretic and β blocker.[20]

An alternative option is to base combination therapy on outcomes, a trial-based approach. Unfortunately, there are very

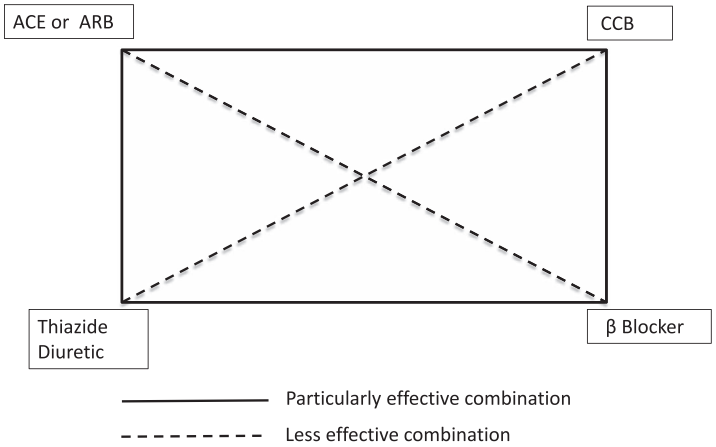


Figure 2. Physiologically based combinations of antihypertensive medications. Combining drugs at the adjacent borders of the figure is particularly effective. ACE: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; CCB: calcium channel blocker. Adapted from Giles and Sander.[21]

few trials in this area. The randomized, double-blind Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial prospectively compared the effects of two antihypertensive combinations—benazepril/hydrochlorothiazide (HCTZ) (force titrated to 40/12.5 mg) and amlodipine besylate/benazepril (force titrated to 5/40 mg)—on the clinical end points of survival and cardiovascular outcomes.[22] ACCOMPLISH enrolled 11,506 patients at high risk for a cardiovascular event, and comorbidities were common. Of the total patients, 50% were obese, 60% had diabetes, 68% were taking lipid-lowering therapy, and 63% were on antiplatelet therapy.

The primary end point in ACCOMPLISH was the time to first event of composite cardiovascular morbidity and mortality. Cardiovascular morbidity was defined as nonfatal, clinically evident, acute myocardial infarction (MI), nonfatal stroke, hospitalization for unstable angina, resuscitated sudden cardiac death, or coronary revascularization procedures. Cardiovascular mortality was defined as death due to sudden cardiac death, fatal MI, fatal stroke, death due to coronary intervention, or death due to congestive heart failure or other cardiovascular causes.

The amlodipine-based regimen lowered office-based BP slightly more effectively (1 mm Hg), but 24-hour BP control was slightly better (1.6 mm Hg) with the HCTZ-based regimen.[23] Despite the aggressive treatment given to enrolled patients before study randomization (e.g., 75% of patients were treated with two or more antihypertensive agents), only 37.3% were controlled to the BP goal of < 140/90 mm Hg.

In ACCOMPLISH, the risk for the primary end point was reduced by 20% in the group receiving the CCB amlodipine plus the ACE benazapril when compared to the group receiving benazapril plus hydrochlorothiazide (P = .0002). The composite primary end point was driven by fewer fatal and nonfatal MIs in the ACE/CCB group than the ACE/HCTZ group (RR 21.5%, P = .04) and 13.9% reduction in coronary revascularization procedures (P = .04). ACCOMPLISH is the first large-scale randomized trial suggesting that an ACE/CCB-based therapy is superior to an ACE/thiazide-based regimen. ACCOMPLISH has been criticized for its use of HCTZ rather than chlorthalidone, which is known to have superior BP lowering effects and was the thiazide used in most randomized trials.[24] Perhaps most importantly, chlorthalidone is superior to HCTZ for preventing cardiovascular events.[25]

While this is a valid point, in the United States there is currently only one FDA-approved fixed-dose chlorthalidone/ARB combination drug (chlorthalidone/azilsartan). The overwhelming majority of current, clinically available, fixed-dose combination ACE/diuretic products have HCTZ as the diuretic, and despite slightly better 24-hour BP control in ACCOMPLISH with the ACE/HCTZ combination, the ACE/CCB combination had fewer cardiovascular events.

Treatment of African Americans

For every level of BP, African Americans have more target organ damage than other ethnic groups.[26] Because of this, the International Society of Hypertension in Blacks has suggested a goal of < 135/85 mm Hg for that patient population. [27] With the SPRINT results, it is likely that < 130/80 mm Hg will be the target BP in African Americans.

Type 2 Diabetes

Currently, there is lack of consensus regarding the treatment goal for type 2 diabetes. Guidelines from Canada, Japan, and Great Britain recommend a goal of < 130/80 mm Hg,[4,6,20] whereas other countries and societies, including the American Diabetes Association, recommend < 140/90 mm Hg (Table 1). Although SPRINT did not include patients with diabetes, the benefit accrued to those in the intensive-treatment arm will lend support to a goal of < 130/80 mm Hg (Figure 1).

The results from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial was the major impetus for some groups to abandon a goal of < 130/80 mm Hg and promote a goal of < 140/90 mm Hg.[28] ACCORD randomized 4,734 patients with type 2 diabetes to a systolic BP goal of either < 120 mm Hg (intensive therapy) or < 140 mm Hg (standard therapy). The mean duration of follow-up for the rate of death was 5 years. There was no difference in the primary outcome, which was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular disease (1.87%/year vs 2.09%/year, intensive vs standard, p = .20). In addition, in the intensive group there was twice the incidence of adverse events, which were primarily reversible metabolic and hypotensive events. Although the secondary outcome of stroke event rate was low in the study, there was a significant reduction in the stroke incidence in the intensive group (0.32% per year vs 0.53%/year, HR 0.59 (95% CI 0.39 – 0.89, p = .01). During a 5-year period, 89 patients would need to be treated to the intensive goal to prevent one stroke.

A suggestion of potential harm from lower BP targets in patients with type 2 diabetes comes from the Randomized Olmesartan And Diabetes Micro-Albuminuria Prevention (ROADMAP) study, in which the primary end point was delay in developing microalbuminuria.[29] Patients were randomized to receive either the ARB olmesartan or placebo, and all patients were treated to a goal BP of < 130/80 mm Hg. After 4 years of treatment, nearly 80% of the patients in the olmesartan group and about 71% of those in the placebo group had a BP < 130/80 mm Hg. The mean BP was 125.7/74.3 mm Hg in the olmesartan group and 128.7/76.2 mm Hg in the placebo group. Patients who received olmesartan showed a significant reduction of new-onset microalbuminuria. However, the olmesartan group had a higher incidence of CV outcomes. A post-hoc analysis (i.e., not prespecified) showed an interaction between pre-existing CAD and achieved BP. Among patients with preexisting CAD, those in either the lowest quartile of systolic BP (< 121.9 mm Hg) or those in the highest quartile of reduction in systolic blood pressure (> 17.3 mm Hg) during the double-blind treatment period had the highest rates of death from cardiovascular causes. Whether this event was by chance, due to a lower blood pressure, or was directly related to olmesartan is not known. As the authors state: "Therefore, excessive reduction of blood pressure in some high-risk patients may confer a predisposition to an increased risk of death, a finding that is consistent with the well-known, somewhat controversial 'J-curve effect'; however, a direct effect of olmesartan cannot be ruled out."

Those who advocate for a goal of < 130/80 mm Hg site three trials: HOT, ABCD, and ACCORD. In the Hypertension Optimal Treatment (HOT) study, participants with diabetes who were randomized to a diastolic BP goal of < 80 mm Hg (achieved 82.6 mm Hg) had a 50% reduction in major CV events compared to those randomized to the diastolic BP goal of < 90 mm Hg.[30] The Appropriate Blood Pressure Control in Diabetes (ABCD) study was designed to evaluate the effect of intensive versus moderate diastolic BP control on vascular and renal complications in 480 normotensive patients with type 2 diabetes and stage 2 CKD.[31] Patients were randomized to one of two BP target groups: either

a moderate diastolic BP goal of 80 to 89 mm Hg, or a goal of 10 mm Hg below the baseline diastolic BP. After a mean follow-up of 5.3 years, the BPs in the two groups were 137/81 mm Hg and 128/75 mm Hg, respectively ($P < .001$). Fewer patients in the intensively treated group progressed from normo- to microalbuminuria ($P = .012$) and micro- to overt albuminuria ($P = .028$). There was less progression of diabetic retinopathy ($P = .019$) and a lower incidence of strokes ($P = .03$). Those who use ACCORD to advocate for the goal of < 130/80 mm Hg make two points.[4] First, they argue that in ACCORD the secondary outcome of fewer strokes was achieved with the lower BP goal. Second, they note that there was significant interaction between BP and glycemic control such that those with the lower BP target who were in the usual-care glycemia group (A1c 7-8%) had a significant improvement in primary outcome. SPRINT will bolster the arguments of those who advocate a BP goal of < 130/80 mm Hg in patients with diabetes.

Chronic Kidney Disease

Most organizations and guidelines are currently recommending a target of < 140/90 mm Hg in patients with CKD and it is unlikely that the SPRINT results will change this (Figure 1, Table 1). In the SPRINT patients with CKD, the renal outcome was a composite of a decrease in the estimated glomerular filtration rate of 50% or more or the development of end-stage renal disease (ESRD) requiring long-term dialysis or kidney transplantation. There was no difference in the primary renal outcome in CKD patients who were in the intensive-treatment arm compared to those in the standard-treatment arm.

When CKD is accompanied by urinary excretion of > 300 mg protein/24 hours, a lower goal of < 130/80 mm Hg may be warranted. A urinary protein/24 hours of ≥ 300 mg/dL corresponds to a urinary protein/urinary creatinine (P:C) ratio of > .22 or a spot urine P:C ratio of > 300 mg/g.[32] Data for this lower goal comes from the African American Study of Kidney Disease and Hypertension (AASK), which randomized 1,094 African Americans with a glomerular filtration rate between 20 and 65 mL/min/m^2 to an intensive BP goal of mean arterial pressure (MAP) < 92 mm Hg (BP ~125/75 mm Hg) and a usual goal of MAP 102 to 107 mm Hg (~140/90 mm Hg). Although there was no difference in the composite outcome (renal function decline, end-stage renal disease, or death) between the randomized groups at the end of 5 years, the patients continued to be followed as a cohort. At the end of 10 years, those who were initially assigned to the intensive arm had better outcomes only if their baseline P:C ratio was > .22.[33] Since the absolute reduction in events was 10%, only 10 patients with this level of proteinuria need to be treated over 10 years to achieve benefit. In those with a P:C ratio ≤ .22, there was no difference in outcome between the intensive and standard group. Importantly, the more intensively treated group did not have more adverse events. Consistent with the findings in AASK, a systematic review in patients with CKD concluded that "evidence does not conclusively show that a currently recommended blood pressure target of less than 130/80 mm Hg improves clinical outcomes more than a conventional target of less than 140/90 mm Hg in adults with CKD. A lower target may be beneficial in persons with proteinuria greater than 300 to 1000 mg/dL."[34] Furthermore, in patients with CKD who have either diabetes (see above), CVD, or CAD (see below), it is likely that a target of < 130/80 mm Hg will be recommended in SPRINT-era guidelines (Figure 1).

Cardiovascular and Coronary Artery Disease

In patients with CAD, most organizations and guidelines currently are recommending a target of < 140/90 mm Hg as opposed to the previous recommendation of < 130/80 mm Hg.[4,6,7] The American Heart Association/American College of Cardiology/American Society of Hypertension guidelines also recommend that "a lower target BP (< 130/80 mm Hg) may be appropriate in some individuals" (Table 1). However, there is only limited data to support a BP goal of < 130/80 mm Hg.

Perhaps the best data for a lower goal came from the CAMELOT trial, where patients with CAD (rather liberally defined as > 20% coronary stenosis) and diastolic BP < 100 mm Hg (average BP 129/78 mm Hg) were randomized to treatment with either amlodipine (CCB) or enalapril (ACE) versus placebo and followed for 24 months.[35] A substudy of 274 patients measured the effect of achieved BP on progression of atherosclerosis as assessed by intravascular ultrasound. Results of the substudy showed that the achieved systolic BP level was associated with progression of coronary atherosclerosis. Individuals with BP in the hypertensive range (average of 147/80 mm Hg) had an increase of 12.0 ± 3.6 mm^3 in atheroma volume, individuals with prehypertension (average of 128/76 mm Hg) had no major change, and those with normal BP levels (average of 114/71 mm Hg) had a decrease of 4.6 ± 2.6 mm^3 in atheroma volume.[36] However, the CAMELOT trial did not randomize patients to these BP goals. The substudy results were based on achieved BP, and the ability of one patient to achieve a lower BP with the same dose of medication may simply reflect the fact that this particular patient had intrinsically healthier vasculature. It would then be expected that this patient would have less-extensive progression of atherosclerosis. Indeed, as was demonstrated in the AASK study, analysis based on achieved BP as opposed to intention-to-treat analysis is fraught with excessive bias and should not be used to inform hypertension guidelines.[37]

Prior to SPRINT, there has not been a large trial that randomized patients with CAD to a usual versus a low BP goal. Therefore, the extent to which BP should be lowered in patients with CAD was previously only informed by observational studies. These studies, which are subject to bias based on analysis of achieved BP, suggest that there is a J-curve with relation to diastolic BP and CV events. In the INVEST study, which compared efficacy of β-blocker strategy versus CCB strategy, there was a nadir in events at an achieved diastolic BP of 84 mm Hg. Below this level, CV event rates began to increase.[38] Similar types of data came from Syst-Eur, which was a study of BP lowering in patients with isolated systolic hypertension. In Sys-Eur, risk began to increase in patients with CAD at an achieved diastolic BP < 80 mm Hg. The hazard ratio was 1.1 at a diastolic of 70 mm Hg, which led the authors to conclude that it was prudent not to lower patients with CAD below that level.[39] As noted above, the ROADMAP study, which randomized patients with type 2 diabetes to receive the ARB olmesartan or placebo, also suggests that a J-curve may exist.[29] Target BP of < 130/80 mg Hg was achieved in nearly 80% of those on olmesartan, and compared to placebo there was a marked and significant reduction in onset of microalbuminuria, the primary end point. However, there were more fatal cardiovascular events in the ARB group. Exploratory analysis found that there was a trend toward higher death rate in those in the lowest quartile and the highest quartile of achieved BP, suggesting that excessive BP lowering and the J-curve effect might have been the cause of increased CV events in the ARB group.[18]

In SPRINT, at one year the BP in the intensive-treatment group was 121.4/68.7 mm Hg and 136.2/76.3 mm Hg in the standard-treatment group. Although SPRINT showed no statistical difference in outcome, those patients with cardiovascular disease in the intensive-treatment group had 17% fewer events, with a hazard ratio of 0.83; confidence interval [CI] 0.62-1.09). This suggests that the lower goal is superior and that a J-curve does not exist unless diastolic BP is lowered below 60 mm Hg. Therefore, it is likely that the new goal for patients with CVD and/or CAD will be lowered to < 130/80 mm Hg (Figure 1).

Management of Patients with Multiple Comorbidities

In clinical practice it is not uncommon to encounter patients with multiple comorbidities. For example, a patient with CKD may have diabetes or CVD. In these situations, the clinician might be faced with two competing BP goals. In a patient with CKD and diabetes, SPRINT-era guidelines could have a CKD goal of < 140/90 mm Hg, whereas the diabetes goal could be < 130/80 mm Hg. To manage these patients practically and extrapolate the evidence in the most rational way, it is the author's opinion that the lower BP goal should be the target (Figure 1).

Conflict of Interest Disclosure: The author has completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement and none were reported.

Keywords: blood pressure, guidelines, masked hypertension, essential hypertension, SPRINT study

References

1. The SPRINT Research Group, A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015 Nov 9. [Epub ahead of print].
2. ESH/ESC Task Force for the Management of Arterial Hypertension. 2013 Practice guidelines for the management of arterial hypertension of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC): ESH/ESC Task Force for the Management of Arterial Hypertension. J Hypertens. 2013 Oct;31(10):1925-38.
3. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014 Feb 5;311(5):507-20.
4. Daskalopoulou SS, Rabi DM, Zamke KB, et al.;for the Canadian Hypertension Education Program. The 2015 Canadian Hypertension Education Program Recommendations for Blood Pressure measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension. Canadian J Cardiol. 2015 May;31(5):549-69.
5. Weber MA, Schiffrin EL, White WB, et al. Clinical practice guidelines for the management of hypertension in the community a statement by the American Society of Hypertension and the International Society of Hypertension. J Hypertens. 2014 Jan;32(1):3-15.
6. Shimamoto K, Ando K, Fujita T, et al; Japanese Society of Hypertension Committee for Guidelines for the Management of Hypertension. The Japanese Society of Hypertension Guidelines for the Management of Hypertension (JSH 2014). Hypertens Res. 2014 Apr;37(4):253-390.
7. Rosendorff C, Lackland DT, Allison M, et al; American Heart Association, American College of Cardiology, American Society of Hypertension. Treatment of hypertension in patients with coronary artery disease: a scientific statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension. Circulation. 2015 May 12;131(19):e435-70.
8. American Diabetes Association. Cardiovascular disease and risk management. Sec. 8. Diabetes Care. 2015 Jan;38(Suppl 1):S49-S57.
9. Hypertension Detection and Follow-up Cooperative Group, Five-year findings of the Hypertension Detection and Follow-up Program: I. Reduction in mortality of persons with high blood pressure, including mild hypertension. J Am Med Assoc, 1979 Dec 7;242(23);2562-71.
10. MRC trial of treatment of mild hypertension: principal results. Medical Research Council Working Party. Br Med J (Clin Res Ed). 1985 Jul 13;291(6488):97-104.
11. The Australian therapeutic trial in mild hypertension. Report by the Management Committee. Lancet. 1980 Jun 14;1(8181):1261-7.
12. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP Cooperative Research Group. JAMA. 1991 Jun 26;265(24):3255-64.
13. Beckett NS, Peters R, Fletcher AE, et al.; HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. N Engl J Med. 2008 May 1;358(18):1887-98.
14. Perry HM Jr, Davis BR, Price TR, et al. Effect of treating isolated systolic hypertension on the risk of developing various types and subtypes of stroke: The Systolic Hypertension in the Elderly Program (SHEP). JAMA. 2000 Jul 26;284(4):465-71.
15. Wright JT Jr, Fine LJ, Lackland DT, Ogedegbe G, Dennison Himmelfarb CR. Evidence supporting a systolic blood pressure goal of less than 150 mm Hg in patients aged 60 years or older: the minority view. Ann Intern Med. 2014 Apr 1;160(7):499-503.
16. Krakoff LR, Gillespie RL, Ferdinand KC, et al. 2014 hypertension recommendations from the eighth joint national committee panel members raise concerns for elderly black and female populations. J Am Coll Cardiol. 2014 Jul 29;64(4):394-402.
17. Murthy VL, Shah RV, Rubenfire M, Brook RD. Comparison of the Treatment Implications of American Society of Hypertension and International Society of Hypertension 2013 and Eighth Joint National Committee Guidelines: an analysis of National Health and Nutrition Examination Survey. Hypertension. 2014 Aug;64(2):275-80.
18. Ambrosius WT, Sink KM, Foy CG, et al; SPRINT Study Research Group. The design and rationale of a multicenter clinical trial comparing two strategies for control of systolic blood pressure: the Systolic Blood Pressure Intervention Trial (SPRINT). Clin Trials. 2014 Oct;11(5):532-46.
19. Mossello E, Pieraccioli M, Nesti N, et al. Effects of low blood pressure in cognitively impaired elderly patients treated with antihypertensive drugs. JAMA Intern Med. 2015 Apr;175(4):578-85.
20. National Institute for Health and Clinical Excellence (NICE) [Internet]. London, UK: NICE; c 2014. Hypertension: Clinical management of primary hypertension in adults. NICE guidelines [CG127]. 2011 Aug [cited 2015 Aug 21]. Available from: http://www.nice.org.uk/guidance/CG127.
21. Giles TD, Sander GE. Beyond the usual strategies for blood pressure reduction: therapeutic considerations and combination therapies. J Clin Hypertens (Greenwich). 2001 Nov-Dec;3(6):346-53.
22. Jamerson K, Weber MA, Bakris GL, et al; ACCOMPLISH Trial Investigators. Benazepril plus amlodipine or hydrochlorothiazide

for hypertension in high-risk patients. N Engl J Med. 2008 Dec 4;359(23):2417-28.
23. Jamerson KA, Devereux R, Bakris GL, et al. Efficacy and duration of benazepril plus amlodipine or hydrochlorothiazide on 24-hour ambulatory systolic blood pressure control. Hypertension. 2011 Feb;57(2):174-9.
24. Ernst ME, Carter BL, Basile JN. All thiazide-like diuretics are not chlorthalidone: putting the ACCOMPLISH study into perspective. J Clin Hypertens (Greenwich). 2009 Jan;11(1):5-10.
25. Roush GC, Holford TR, Guddati AK. Chlorthalidone compared with hydrochlorothiazide in reducing cardiovascular events: systematic review and network meta-analyses. Hypertension. 2012 Jun;59(6):1110-7.
26. Klag MJ, Whelton PK, Randall BL, Neaton JD, Brancati FL, Stamler J. End-stage renal disease in African-American and white men. 16-year MRFIT findings. JAMA. 1997 Apr 23-30;277(16):1293-8.
27. Flack JM, Sica DA, Bakris G, et al. Management of high blood pressure in blacks. Hypertension. 2010 Nov;56(5):780-800.
28. Cushman WC, Evans GW, Byington RP, et al; ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010 Apr 29;362(17):1575-85.
29. Haller H, Ito S, Izzo JL Jr, et al; ROADMAP Trial Investigators. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. N Engl J Med. 2011 Mar 10;364(10):907-17.
30. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet. 1998 Jun 13;351(9118):1755-62.
31. Schrier RW, Estacio RO, Esler A, Mehler P. Effects of aggressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kidney Int. 2002 Mar;61(3):1086-97.
32. Weinstock Brown W, Keane WF. Proteinuria and cardiovascular disease. Am J Kidney Dis. 2001 Oct;38(4 Suppl 1):S8-S13.
33. Appel LJ, Wright JT Jr, Greene T, et al; AASK Collaborative Research Group. Intensive blood-pressure control in hypertensive chronic kidney disease. N Engl J Med. 2010 Sep 2;363(10):918-29.
34. Upadhyay A, Earley A, Haynes SM, Uhlig K. Systematic review: blood pressure target in chronic kidney disease and proteinuria as an effect modifier. Ann Intern Med. 2011 Apr 19;154(8):541-8.
35. Nissen SE, Tuzcu EM, Libby P, et al; CAMELOT Investigators. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. JAMA. 2004 Nov 10;292(18):2217-25.
36. Sipahi I, Tuzcu EM, Schoenhagen P, et al. Effects of normal, pre-hypertensive, and hypertensive blood pressure levels on progression of coronary atherosclerosis. J Am Coll Cardiol. 2006 Aug 15;48(4):833-8.
37. Davis EM, Appel LJ, Wang X, et al; African American Study of Kidney Disease and Hypertension Research Collaborative Group. Limitations of analyses based on achieved blood pressure: lessons from the African American study of kidney disease and hypertension trial. Hypertension. 2011 Jun;57(6):1061-8.
38. Messerli FH, Mancia G, Conti CR, et al. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? Ann Intern Med. 2006 Jun 20;144(12):884-93.
39. Fagard RH, Staessen JA, Thijs L, et al. On-treatment diastolic blood pressure and prognosis in systolic hypertension. Arch Intern Med. 2007 Sep 24;167(17):1884-91.