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What is adequate hypertension control? Having your dinner and dessert too

ABSTRACT

Now that many options for treating hypertension are available and the studies of their use have proliferated, selecting a specific antihypertensive agent for a specific condition often receives an inordinate amount of attention from physicians. Controlling the blood pressure per se should be our primary concern ("dinner"), while choosing agents that may have added benefit in specific situations is secondary ("dessert").

KEY POINTS

Measurements by the physician in the office may not be the most accurate way to assess blood pressure; ambulatory monitoring and home self-measurements may be better.

The goal blood pressure for most patients younger than 80 years is less than 140/90 mm Hg. The goal should be lower if the patient also has diabetes, renal disease, or cardiovascular disease.

Additional benefits can be obtained by incorporating specific antihypertensive agents (eg, angiotensin-converting enzyme inhibitors) in the regimens of patients with diabetes, proteinuria, or cardiovascular disease.

A 65-YEAR-OLD WOMAN with a 6-year history of adult-onset diabetes mellitus presents to your office with a blood pressure of 156/94 mm Hg confirmed on three separate visits, heart rate 72 beats per minute, and body mass index 33.4. She has no findings on physical examination to suggest a secondary form of hypertension. Her low-density lipoprotein cholesterol (LDL-C) concentration is 176 mg/dL, and a spot urinalysis indicates that her predicted 24-hour protein excretion is 1,786 mg. The rest of her laboratory evaluation is normal.

What to do? This patient is the poster child for a syndrome primary care physicians see every day: hypertension with multiple risk factors for cardiovascular disease and death, all rooted in the rising epidemic of obesity.¹ Many guidelines are available,²⁻⁷ and all broadly agree that the practitioner must:

- Determine whether the patient truly has hypertension
- Decide on the appropriate blood pressure goal
- Assess whether compelling indications exist to incorporate specific antihypertensive agents into the patient's regimen.

This last task—selecting a specific agent with perceived benefit in a specific condition, such as an angiotensin-converting enzyme (ACE) inhibitor in proteinuria—tends to receive an inordinate amount of attention. If we compare treating hypertension to eating a meal, the "dinner" is lowering the blood pressure to the appropriate goal level. Selecting a specific class of agent for a specific concomitant condition is the "dessert."

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And just as we should not skip dinner and eat only dessert, in treating hypertension we should not just prescribe the right drug for the concomitant condition and neglect the blood pressure goal.

■ GUIDELINES HAVE EVOLVED

The guidelines for diagnosing and treating hypertension have evolved over the past 2 decades.

Take, for example, the Joint National Committee (JNC) guidelines. In 1984, the JNC 3 report² stated that a systolic blood pressure of up to 159 mm Hg was acceptable in elderly patients. In 2003, however, the JNC 7 report⁷ recommended lowering blood pressure to less than 140/90 mm Hg in the elderly, as in all other patients with hypertension.

Another change in JNC 7 that further emphasized the danger of high blood pressure is that the upper limit of normal was lowered and a new diagnosis was created: “prehypertension” (TABLE 1). JNC 7 also recommended using lower blood pressure targets in certain subgroups of patients with hypertension (TABLE 2).

Practice patterns have not kept up with the guideline changes. The Systolic Hypertension in the Elderly study⁸ showed that only 30% of general practitioners, 38% of internists, and 58% of cardiologists were willing to treat to the aggressive targets outlined in the JNC 7 guidelines.

Should hypertension be defined by other risk factors?

JNC 7 had the unintended consequence of leading to calls for further changes in the definition of hypertension. Giles et al⁹ offer an approach in which patients with risk factors (eg, diabetes mellitus, microalbuminuria) would be treated for hypertension if their blood pressure is greater than 120/80! This approach is similar to that of the European Society of Hypertension and European Society of Cardiology (ESH/ESC) guidelines,¹⁰ except the ESH/ESC uses fixed values for blood pressure to which risk factors are added to yield a treatment strategy.

Others recognize the importance of cardiovascular risk factors in decision-making but oppose this new definition of hypertension

TABLE 1

Changes in blood pressure classification from JNC 6 to JNC 7

JNC 6 CATEGORY ^a	SYSTOLIC	DIASTOLIC	JNC 7 CATEGORY ^b
Optimal	< 120	< 80	Normal
Normal	120–129	80–84	Prehypertension
Borderline	130–139	85–89	Prehypertension
Hypertension	≥ 140	≥ 90	Hypertension
Stage 1	140–159	90–99	Stage 1
Stage 2	160–179	100–109	Stage 2
Stage 3	≥ 180	≥ 110	Stage 2

^aBlack HR, Cohen JD, Kaplan NM, et al. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Arch Intern Med 1997; 157:2413–2446.

^bChobanian 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; 289:2560–2572.

because it needlessly complicates the approach to hypertension management.¹¹ Of the guidelines, those of the ESH/ESC and the JNC 6 report (1997)⁵ best integrate blood pressure and target organ involvement as the primary and secondary factors, respectively, in clinical decision-making. This integration was lost in JNC 7 in the interest of simplicity, and JNC 7 is the worse for its removal.

■ START WITH ACCURATE MEASUREMENT

Something that we often forget is that, to reach goal blood pressure, we need to know what the patient’s blood pressure is. Accurate measurement is especially important with the lower blood pressure targets that are desirable in hypertensive patients with renal disease, diabetes, and cardiovascular disease.

Measurement of blood pressure by the physician in the office has several limitations. Evidence exists that many physicians are poorly trained to take blood pressure,¹² frequently demonstrate “digit preference” (eg, a preference for pressure readings ending in 0 or 5),¹³ and can induce the white-coat effect (higher pressures in the physician’s office than in the patient’s usual environment),¹⁴ all of

The ‘dinner’ in treating hypertension is getting blood pressure to goal levels

TABLE 2

JNC 7 target blood pressures

CONDITION	TARGET (MM HG)
Uncomplicated hypertension	< 140/90
Diabetes	< 130/85
Cardiovascular disease	< 130/85
Renal disease	
Without proteinuria	< 130/85
With > 1 g of proteinuria	< 125/75

DATA 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; 289:2560-2572.

which can affect the accuracy of the measurements.

Newer methods of blood pressure measurement might be better than auscultatory blood pressure measurements performed by the doctor. Multiple automated blood pressure measurements using the oscillometric method can reduce observer errors such as digit preference,¹⁵ decrease the white-coat effect,¹⁶ and provide accuracy equal to that of the trained observer.¹⁷ Twenty-four-hour ambulatory blood pressure monitoring has a stronger correlation with target organ damage than office blood pressure measurement and is an important tool in assessing antihypertensive therapy.^{18,19} Home automated blood pressure measurement can enhance blood pressure control,²⁰ improve adherence,²¹ and reveal masked hypertension²² (normal clinic blood pressure with elevated ambulatory or home blood pressure, which has been shown to impart the same high risk of cardiovascular events as poorly controlled hypertension²³).

Using these newer forms of blood pressure measurement in addition to office auscultatory blood pressure readings enhances both the diagnosis and the treatment of hypertension.

■ REACHING TARGET BLOOD PRESSURE IS THE 'DINNER'

Having decided that our 65-year-old patient indeed has an elevation of blood pressure that demands therapy, to what level should we lower her blood pressure?

TABLE 2 shows the current JNC 7 treatment targets for uncomplicated hypertension and for hypertension complicated by other cardiovascular risk factors.

Many studies showed that lowering blood pressure to less than 140/90 mm Hg with anti-hypertensive drugs is safe, effective, and achievable in up to 60% of hypertensive patients younger than 80 years.²⁴⁻²⁶ For patients older than 80 years, however, the evidence of benefit of lowering blood pressure to this target is insufficient. In fact, some evidence suggests that lowering blood pressure in a patient 80 years or older may be imprudent, as high blood pressure at that age may not be associated with increased risk of death.²⁷ Further clarification of the optimal treatment of elderly patients awaits the outcome of the ongoing Hypertension in the Very Elderly Trial in Europe.²⁸

Of note: the new definition of "normal" blood pressure (< 120/80 mm Hg) introduced by JNC 7 is not the new treatment target. Although lifestyle modifications that lower blood pressure to less than 120/80 mm Hg in patients with prehypertension (121-139 mm Hg systolic, 81-89 mm Hg diastolic) are recommended since they are inherently safe,²⁹ there is no evidence that drug therapy to this target is also safe. This point is important, as several studies have shown that two or three agents are required on average to lower blood pressure to near this level.^{24,30} Adding more drugs to get to this target increases the risk of side effects and raises the concern that excessive reduction of diastolic blood pressure might actually increase the risk of death.³¹

In Britain, a less aggressive approach

The British Hypertension Society (BHS)³² takes a less aggressive approach than JNC 7. The latest BHS guidelines recommend starting antihypertensive therapy if the sustained systolic blood pressure is at least 160 mm Hg or the diastolic blood pressure is at least 100 mm Hg. If the systolic blood pressure is 140 to 159 mm Hg or if the diastolic pressure is 90 to 99 mm Hg, the accompanying cardiovascular risk factors must combine to impose an estimated cardiovascular risk of greater than 20% in the next 10 years to justify starting blood-pressure-lowering medications.

**Automated
blood pressure
readings may
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physician
readings**

The BHS also differs in its treatment target, which is less than 140/85 mm Hg. However, their “audit standard” (minimal acceptable level of control³²) is achievement of a systolic blood pressure less than 150 and a diastolic pressure less than 90. The BHS bases these targets solely on its interpretation of the Hypertension Optimal Treatment (HOT) trial data.²⁴

The consensus is that after hypertension is diagnosed using office measurements and newer methods such as home self-measurement or ambulatory monitoring, the target of treatment in hypertensive patients younger than 80 years should be a blood pressure lower than 140/90 mm Hg in the office or less than 135/85 by home self-measurement or daytime ambulatory monitoring. Only significant orthostatic hypotension would deter the clinician from this goal.

■ LOWER TARGETS IN PATIENTS AT HIGHER RISK

Lower blood pressure targets seem justified in several conditions (TABLE 2), in view of improved outcomes if these targets are used. Let's examine the evidence for these lower blood pressure goals.

Diabetes mellitus

Several hypertension trials, such as the Multiple Risk Factor Intervention Trial (MRFIT),³³ the Systolic Hypertension in the Elderly Program (SHEP),³ and the Systolic Hypertension in Europe (Syst-Eur) trial,²⁶ have shown that lowering blood pressure in diabetic hypertensive patients reduces cardiovascular morbidity and mortality rates more than the same degree of blood pressure reduction in patients without diabetes.

Evidence that lowering blood pressure to targets lower than 140/90 mm Hg is beneficial in patients with diabetes comes from two studies:

In the United Kingdom Prospective Diabetes Study,³⁴ diabetic patients assigned to “tight” blood pressure control (mean achieved blood pressure 144/82 mm Hg) did better than those who had standard control of blood pressure. The reduction in cardiovascular risk from tight blood pressure control was larger than that seen with tight glycemic control.

Furthermore, subgroup analysis of the 1,501 patients with diabetes in the HOT trial revealed that those who were randomized to a goal diastolic blood pressure of less than 80 mm Hg had 51% fewer cardiovascular events than those with a goal of less than 90 mm Hg.²⁴

Thus, current treatment targets for diabetic patients are less than 130/85 mm Hg (JNC 7), or less than 130/80 (American Diabetes Association³⁵ and ESH/ESC¹⁰). Here again, the BHS guidelines differ significantly from other guidelines, allowing a higher audit standard of less than 140/80 mm Hg.³²

Renal disease

The most important factor in preservation of renal function in chronic kidney disease, especially proteinuric renal disease, is lowered blood pressure. While the Modification of Diet in Renal Disease (MDRD) study found that restricting dietary protein intake had little benefit, it did show that aggressive blood pressure reduction was more effective than standard reduction in slowing the progression of renal failure.³⁶ The authors suggested that for patients with proteinuria of more than 1 g/day, a target office blood pressure of less than 125/75 mm Hg should be used; for those with proteinuria of 0.25 to 1 g/day, a target of less than about 130/80 may be advisable.

Subsequently, the Irbesartan Diabetic Nephropathy Trial (IDNT) showed that if the systolic blood pressure was less than 149 mm Hg, the risk of doubling of serum creatinine or onset of end-stage renal disease was 2.2 times higher than if the systolic blood pressure was less than 134 mm Hg.³⁷ Furthermore, lowering systolic blood pressure to as low as 120 mm Hg improved patient and renal survival, independent of baseline renal function at study entry. Reductions in systolic blood pressure below this level, however, were associated with a worsening of renal survival.

The Appropriate Blood Pressure Control in Diabetes (ABCD) study confirmed the benefit of aggressive blood pressure control in reducing proteinuria in patients with diabetes and renal disease.³⁸

On the other hand, initial reports from the African American Study of Kidney

‘Normal’ blood pressure (120/80) is not the goal of drug treatment

TABLE 3

Indications for specific classes of antihypertensive agents

DISEASE	ANTIHYPERTENSIVE AGENTS
Diabetes mellitus	Angiotensin-converting enzyme (ACE) inhibitors Angiotensin receptor blockers
Myocardial infarction	Beta-blockers ACE inhibitors
Congestive heart failure	Beta-blockers ACE inhibitors Angiotensin receptor blockers Aldosterone inhibitors
Proteinuria	ACE inhibitors Angiotensin receptor blockers Non-dihydropyridine calcium channel blockers
After angioplasty	Beta-blockers

Some studies say that blood pressure-lowering per se matters more than the drug used

Disease (AASK) did not show a benefit of aggressive reduction in blood pressure,³⁰ but a second subgroup analysis did find that the low blood pressure group treated with amlodipine did have a reduced risk of end-stage renal disease or death, a finding not seen with the other antihypertensive agents in the trial.³⁹

Further data contradicting the hypothesis that lower blood pressure is better in renal disease comes from the Ramipril Efficacy in Nephropathy Trial (REIN-2), in which no difference in time to end-stage renal disease was seen in patients initially treated with ramipril, regardless of whether they underwent intensified or standard blood pressure reduction.⁴⁰

Cardiovascular disease

Epidemiologic studies clearly show that the risk of cardiovascular disease begins to increase with increments in blood pressure at lower levels than those considered to be hypertensive.⁴¹ These observations led to the concept of prehypertension found in JNC 7.

In the HOT trial,²⁴ aggressive reduction in diastolic blood pressure reduced the num-

ber of myocardial infarctions but did not further reduce the rates of other cardiovascular events. Nevertheless, the results of this study are the basis for recommendations of lower blood pressure targets in patients with known cardiovascular disease.

Concern about lower targets in this group has come from two recent studies. First, in IDNT,⁴² for every 10 mm Hg decrement in diastolic blood pressure that occurred on treatment, the relative risk of myocardial infarction was increased by 61%, bringing back to life the “J-curve” hypothesis. Furthermore, in reviewing the International Verapamil-Trandolopril Study (INVEST), Messerli et al⁴³ found a nadir in the risk of death or myocardial infarction at an achieved blood pressure of 119/84 mm Hg.

A review article by Birns et al⁴⁴ raises similar concerns about excessive blood pressure reduction in patients with cerebrovascular disease.

The ongoing Secondary Prevention of Small Subcortical Strokes study⁴⁵ is investigating, in patients with a previous lacunar infarct, whether standard blood pressure reduction (systolic pressure 130–149 mm Hg) or intensive reduction (systolic pressure < 130 mm Hg) is better for reducing the risk of recurrent stroke or loss of cognitive function.

■ DESSERT: SPECIFIC DRUGS IN SPECIFIC SITUATIONS

Specific antihypertensive agents have additional clinical benefit beyond blood pressure-lowering in a number of diseases or clinical circumstances (TABLE 3).

In particular, drugs that inhibit the renin-angiotensin-aldosterone system have been found to be beneficial in a variety of diseases. A careful review by Jafar et al⁴⁶ demonstrated conclusively the benefit of ACE inhibition in nondiabetic proteinuric renal disease. A similar benefit from angiotensin receptor blockers³⁷ has been clearly demonstrated. The Heart Outcomes Prevention Evaluation (HOPE) study showed a reduction in cardiovascular risk beyond that expected from blood pressure reduction in high-risk hypertensive patients receiving an ACE inhibitor,⁴⁷ an effect that was even greater in the subpopulation of diabetic subjects.⁴⁸

Why are these unique properties relegated to the role of dessert? First, all studies confirm the primacy of achieving goal blood pressure in reducing cardiovascular disease or slowing the progression of renal failure.

Second, analysis of the HOT, ALLHAT, and AASK trials has shown that three antihypertensive agents on average are required to reach goal blood pressure when blood pressure targets are less than 140/90 mm Hg or in patients at high risk of cardiovascular disease. Thus, important individual agents (eg, ACE inhibitors) that have additional cardiovascular benefits beyond blood pressure reduction can be incorporated within the expected three-drug regimen that will be required to reach goal blood pressure in these patients.

Third, some studies support the concept that blood pressure reduction alone, and not the individual antihypertensive agents that were used, is the most important element in reducing cardiovascular risk in hypertensive patients.^{49,50}

The choice of specific agents may be important in hypertension management in avoiding side effects and in the ability to combine two medications in one pill. Clearly, using a beta-blocker in a young

marathoner with mild hypertension would be a mistake, as it would likely reduce her ability to achieve peak exercise performance. Diuretics are confirmed in their importance in the treatment of hypertension because they can be combined with many drug classes to achieve improved adherence to chronic therapy by reducing the number of pills needed to control blood pressure.

■ CASE REVISITED

In the case presented, the patient's goal blood pressure is less than 125/75 mm Hg because she has proteinuric renal disease and diabetes mellitus.

Achieving treatment targets in hypertension requires a disciplined approach to therapy. The menu for success presented here is based on accurate office and out-of-office measurement (at home and ambulatory); reduction of blood pressure to less than 140/90 mm Hg in all patients younger than 80 years; recognition of subgroups of patients with lower target pressures; and, finally, incorporation of specific antihypertensive agents in unique clinical conditions. This will allow us to achieve maximum benefit in the treatment of hypertension in the patients we serve. ■

■ REFERENCES

1. Mokdad AH, Sordula MK, Dietz WH, Bowman BA, Marks JS, Koplan JP. The spread of the obesity epidemic in the United States, 1991–1998. *JAMA* 1999; 282:1519–1522.
2. The 1984 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1984; 144:1045–1057.
3. SHEP Cooperative Research Group. 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). *JAMA* 1991; 265:3255–3264.
4. Hansson L, Lindholm LH, Ekblom T, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity the Swedish Trial in Old Patients with Hypertension-2 study. *Lancet* 1999; 354:1751–1756.
5. Black HR, Cohen JD, Kaplan NM, et al. The sixth report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure. *Arch Intern Med* 1997; 157:2413–2446.
6. Khan NA, McAlister FA, Rabkin SW, et al; Canadian Hypertension Education Program. The 2006 Canadian Hypertension Education Program recommendations for the management of hypertension: part II—therapy. *Can J Cardiol* 2006; 22:583–593.
7. Chobanian AV, Bakris GL, Black HR, et al; National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003; 289:2560–2572.
8. Doctor's Guide News. Controlling elevated systolic blood pressure in elderly not primary focus among physicians. www.docguide.com. Accessed July 25, 2007.
9. Giles TD, Berk BC, Black HR, et al. Expanding the definition and classification of hypertension. *J Clin Hypertens (Greenwich)* 2005; 7:505–512.
10. O'Brien E, Asmar R, Beilin L, et al; European Society of Hypertension Working Group on Blood Pressure Monitoring. European Society of Hypertension recommendations for conventional, ambulatory and home blood pressure measurement. *J Hypertens* 2003; 21:821–848.
11. Pickering TG. Do we really need a new definition of hypertension? *J Clin Hypertens (Greenwich)* 2005; 7:702–704.
12. Graves JW, Sheps SG. Does evidence-based medicine suggest that physicians should not be measuring blood pressure in the hypertensive patient? *Am J Hypertens* 2004; 17:354–360.
13. Wen SH, Kramer MS, Hoey J, Hanley JA, Usher RH. Terminal digit preference, random error, and bias in routine clinical measurement of blood pressure. *J Clin Epidemiol* 1993; 46:1187–1193.
14. Mancia G, Bertinieri G, Grassi G, et al. Effects of blood pressure measurement by the doctor on patient's blood pressure and heart rate. *Lancet* 1983; 2:695–698.
15. Hla KM, Vokaty KA, Feussner JR. Observer error in systolic blood pressure measurement in the elderly. A case for automated recorders? *Arch Intern Med* 1986; 146:2373–2376.

16. Culleton BF, McKay DW, Campbell NR. Performance of the automated BpTRU measurement device in the assessment of white-coat hypertension and white-coat effect. *Blood Press Monitor* 2006; 11:37–42.
17. Graves JW, Nash C, Burger K, Bailey K, Sheps SG. Clinical decision-making in hypertension using an automated (BpTRU) measurement device. *J Hum Hypertens* 2003; 17:823–827.
18. Perloff D, Sokolow M, Conway R. The prognostic value of ambulatory blood pressure. *JAMA* 1983; 249:2792–2798.
19. Verdecchia P, Porcellati C, Schillaci G, et al. Ambulatory blood pressure. An independent predictor of prognosis in essential hypertension. *Hypertension* 1994; 24:793–801. Correction in *Hypertension* 1995; 25:462.
20. Canzanella VJ, Jensen PL, Schwartz LL, Worra JB, Klein LK. Improved blood pressure control with a physician-nurse team and home blood pressure measurement. *Mayo Clin Proc* 2005; 80:31–36.
21. Canzanella VJ, Jensen PL, Hunder I. Rapid adjustment of antihypertensive drugs produces a durable improvement in blood pressure. *Am J Hypertens* 2001; 14:345–350.
22. Stergiou GS, Salgami EV, Tzamouranis DG, Roussias LG. Masked hypertension assessed by ambulatory blood pressure versus home blood pressure monitoring: is it the same phenomenon? *Am J Hypertens* 2005; 18:772–778.
23. Bobrie G, Chatellier G, Genes N, et al. Cardiovascular prognosis of “masked hypertension” detected by blood pressure self-measurement in elderly treated hypertensive patients. *JAMA* 2004; 291:1342–1349.
24. Hansson L, Zanchetti A, Carruthers SG, et al. Effect of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. HOT Study Group. *Lancet* 1998; 351:1755–1762.
25. ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients randomized to doxazosin vs chlorthalidone: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA* 2000; 283:1967–1975. Correction in *JAMA* 2000; 288:2976.
26. Staessen JA, Fagard R, Thijs L, et al. Randomised double-blind comparison of placebo and active treatment in older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet* 1997; 350:757–764.
27. van Bommel T, Gussekloo J, Westendorp RG, Blauw GJ. In a population-based prospective study, no association between high blood pressure and mortality after age 85 years. *J Hypertens* 2006; 24:287–292.
28. Bulpitt CJ, Beckett NS, Cooke J, et al; Hypertension in the Very Elderly Trial Working Group. Results of the pilot study for the Hypertension in the Very Elderly Trial. *J Hypertens* 2003; 21:2409–2417.
29. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med* 1997; 336:1117–1124.
30. Wright JT, Bakris G, Greene T, et al; African American Study of Kidney Disease and Hypertension Study Group. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA* 2002; 288:2421–2431. Correction in *JAMA* 2006; 295:2726.
31. Cruickshank JM, Thorp JM, Zacharias FJ. Benefits and potential harm of lowering high blood pressure. *Lancet* 1987; 1:581–584.
32. Williams B, Poulter NR, Brown MJ, et al; BHS Guidelines Working Party, for the British Hypertension Society. British Hypertension Society guidelines for hypertension management 2004 (BHS-IV): summary. *BMJ* 2004; 328:634–640. Correction in *BMJ* 2004; 328:926.
33. Multiple Risk Factor Intervention Trial Research Group. Multiple Risk Factor Intervention Trial. Risk factor changes and mortality results. *JAMA* 1982; 248:1465–1477.
34. Holman R, Turner R, Stratton I, et al. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* 1998; 317:703–713. Correction in *BMJ* 1999; 318:29.
35. American Diabetes Association. Standards of medical care in diabetes—2006. *Diabetes Care* 2006; 29(suppl 1):S4–S42.
36. Peterson JC, Adler S, Burkart JM, et al. Blood pressure control, proteinuria, and the progression of renal disease. The Modification of Diet in Renal Disease Study. *Ann Intern Med* 1995; 123:754–762.
37. Lewis EJ, Hunsicker LG, Clarke WR et al; Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001; 345:851–860.
38. Schrier RW, Estacio RO, Jeffers B. Appropriate Blood Pressure Control in NIDDM (ABCD) trial. *Diabetologia* 1996; 39:1646–1654.
39. Contreras G, Greene T, Agodoa LY, et al; African American Study of Kidney Disease and Hypertension Study Group Investigators. Blood pressure control, drug therapy, and kidney disease. *Hypertension* 2005; 46:44–50.
40. Ruggenti P, Perna A, Loriga G, et al; REIN-2 Study Group. Blood-pressure control for renoprotection in patients with non-diabetic chronic renal disease (REIN-2): multicentre, randomised controlled trial. *Lancet* 2005; 365:939–946.
41. Kshirsagar AV, Carpenter M, Bang H, Wyatt SB, Colindres RE. Blood pressure usually considered normal is associated with an elevated risk of cardiovascular disease. *Am J Med* 2006; 119:133–141.
42. Berl T, Hunsicker LG, Lewis JB, et al; for the Collaborative Study Group. Impact of achieved blood pressure on cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial. *J Am Soc Nephrol* 2005; 16:2170–2179.
43. 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; 144:884–893.
44. Birns J, Markus H, Kalra L. Blood pressure reduction for vascular risk: is there a price to be paid? *Stroke* 2005; 36:1308–1313.
45. Grim R, Pergola P, Hart R, et al. Secondary prevention of small subcortical strokes with BP lowering and antiplatelet therapies: a 2x2 factorial trial (SPS3) [abstract]. *J Hypertens* 2006; 24(suppl 6):S330.
46. Jafar TH, Stark PC, Schmid CH, et al; AIPRD Study Group. Progression of chronic kidney disease: the role of blood pressure control, proteinuria, and angiotensin-converting enzyme inhibition: a patient-level meta-analysis. *Ann Intern Med* 2003; 139:244–252.
47. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med* 2000; 342:145–153. Corrections in *N Engl J Med* 2000; 342:748 and 2000; 342:1376.
48. Heart Outcomes Prevention Evaluation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. *Lancet* 2000; 355:253–259.
49. Lindholm LH, Hansson L, Ekblom T, et al. Comparison of antihypertensive treatments in preventing cardiovascular events in elderly diabetic patients: results from the Swedish Trial in Old Patients with Hypertension-2. STOP Hypertension-2 Study Group. *J Hypertens* 2000; 18:1671–1675.
50. Hansson L, Lindholm LH, Niskanen L, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortality in hypertension: the Captopril Prevention Project (CAPPP). *Lancet* 1999; 353:611–616.

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