Published in final edited form as:

Nat Rev Cardiol. 2011 January ; 8(1): 42–49. doi:10.1038/nrcardio.2010.182.

Blood pressure lowering in patients with diabetes—one level might not fit all

Rhonda M. Cooper-DeHoff,

Department of Pharmacotherapy and Translational Research, College of Pharmacy, P. O. Box 100486, University of Florida, Gainesville, FL 32610-0486, USA

Eric F. Egelund, and

Department of Pharmacotherapy and Translational Research, College of Pharmacy, P. O. Box 100486, University of Florida, Gainesville, FL 32610-0486, USA

Carl J. Pepine

Division of Cardiovascular Medicine, College of Medicine, P. O. Box 100277, University of Florida, Gainesville, FL 32610-0277, USA

Abstract

Hypertension and diabetes mellitus frequently occur together, leading to increased complications and mortality in patients with both these conditions. Blood pressure (BP) goals for patients with diabetes have consistently been more aggressive than for patients without diabetes. Although the benefits of lowering BP are well documented, data to support this more aggressive goal are lacking. In fact, lowering BP might not always be better. We review the available evidence regarding BP treatment in patients with hypertension and diabetes from randomized clinical trials, as well as available observational data. We also consider evidence related to the J-shaped curve, which reflects the relationship between BP and outcomes in patients with diabetes, and make recommendations for treatment of BP on the basis of a patient's individual risk, as opposed to on the basis of aggressive BP targets recommended by global guidelines. In the future, a personalized approach will maximize the benefits from treatment.

Introduction

Elevated blood pressure (BP) has long been recognized as an important component of the constellation of risks for long-term cardiovascular sequelae associated with diabetes mellitus.^{1,2} For almost two decades, BP goals in patients with diabetes have been set more aggressively than in patients without diabetes.^{3–7} The prevailing recommendation for treating BP in patients with diabetes has been 'the lower the better', with no threshold.⁸ This recommendation was spearheaded by landmark clinical trials published in the 1990s that

© 2010 Macmillan Publishers Limited. All rights reserved

Correspondence to: R. M. Cooper-DeHoff, dehoff@cop.ufl.edu.

Competing interests

C. J. Pepine declares an association with the following companies: Abbott Laboratories, Angioblast Systems, AstraZeneca, AtCor Medical, Baxter, Bioheart, Daiichi Sankyo, Eli Lilly, Forest Laboratories, GlaxoSmithKline, Medtelligence, NicOx, Novartis, Pfizer, Sanofi-Aventis, Schering-Plough, and SLACK Incorporated. See the article online for full details of the relationships. R. M. Cooper-DeHoff and E. F. Egelund declare no competing interests.

Author contributions R. M. Cooper-DeHoff contributed to discussion of content for the article, researched data to include in the manuscript, wrote the article, reviewed and edited the manuscript before submission, and revised the manuscript in response to the peer-reviewers' comments. E. F. Egelund researched data to include in the manuscript and wrote the article. C. J. Pepine contributed to discussion of content for the article and reviewed and edited the manuscript before submission.

established clear benefit with regard to cardiovascular risk reduction when BP was lowered intensively in patients with diabetes.^{9,10} However, data from more contemporary populations with hypertension and diabetes do not confirm the benefit of intensive BP lowering.^{11,12} In this review, we examine the evidence leading up to the recommendations that ‘lower is better’ with regard to BP lowering, as well as current evidence suggesting that ‘lower is not always better’ for reduction of cardiovascular-related morbidity and mortality. Furthermore, we propose some explanations for the discrepancies that have been observed with regard to the beneficial effects of BP lowering, and provide suggestions for future consideration by guideline committees and practitioners caring for the growing population of patients with hypertension and diabetes.

Diabetes and hypertension

The prevalence of diabetes has increased steadily over the past 40 years, with an estimated 216 million people worldwide developing the disease in the past two decades alone.¹³ By the year 2030, the number of people with diabetes is expected to have risen to 366 million worldwide.¹⁴ As many as 70% of people aged >40 years who have diabetes are also affected by hypertension, with black and Hispanic individuals affected disproportionately compared with the rest of the population.^{15–18} Hypertension and diabetes have an additive effect on long-term cardiovascular risk, with the combination of these conditions leading to greater risk of microvascular complications, including nephropathy and retinopathy, and macrovascular complications such as atherosclerosis and medial calcification.¹⁹ An increased risk of mortality is also observed in patients with diabetes, with eight out of 10 patients with diabetes dying from cardiovascular-related events.²⁰ In fact, common genetic and environmental precursors have been suggested for diabetes and atherosclerosis, which is the basis for the ‘commonsoil hypothesis’ relating to diabetes and cardiovascular disease (CVD).²¹

The inter-related pathophysiology of hypertension and diabetes is complex and not fully understood; however, impaired autoregulation of BP and attenuation of nocturnal decrease in BP have been postulated to have an important role in this process.¹⁸ Comorbidities, such as obesity and dyslipidemia, further complicate the ability to find common pathological mechanisms between the two conditions.^{2,22,23} A twofold to threefold increase in the risk of cardiovascular-related morbidity and mortality is found at every increase in systolic or diastolic BP above 120/80 mmHg;²⁴ in patients with diabetes there is a continuous increase in risk regardless of BP level.^{1,25}

The benefits of treating these conditions are well documented, and the degree of benefit derived is directly proportional to the level of risk when treatment is initiated, regardless of whether diabetes is present.²⁶ From the time when diabetes was established as carrying the same risk of a subsequent cardiovascular event as heart disease, a decade ago,²⁷ guidelines for the management of risk factors in this patient group have evolved to include aggressive lowering of BP;^{6,28,29} however, supporting evidence for this aggressive management of BP in patients with diabetes remains scarce.^{30,31}

Key points

- Diabetes mellitus and hypertension are common comorbid conditions, and are associated with morbidity and mortality related to vascular disease
- Blood pressure (BP) lowering is associated with reduction in cardiovascular-related morbidity and mortality

- Current guidelines recommend a BP goal of <130/80 mmHg in patients with diabetes despite lack of evidence from clinical trials to support this goal
- A J-shaped relationship exists between BP and cardiovascular risk, which seems to be most profound in patients with cardiovascular disease
- Risk management in a patient with diabetes should include selection of a BP-lowering goal that is based on individual level of risk, together with an approach that focuses on the patient as a whole
- Lowering BP to <140/90 mmHg in all patients, regardless of diabetes status, is warranted on the basis of current evidence

Macrovascular benefit of BP lowering

Reduction of BP in patients with hypertension (>140/90 mmHg) and diabetes is known to reduce the risk of cardiovascular events. The studies summarized in Tables 1–3 followed patients over the past two decades; importantly, baseline age, percentage of patients with CVD, and mean BP varied substantially across the studies. This fundamental variation in baseline characteristics could explain some of the observed differences in long-term outcomes. Furthermore, new risk-lowering treatments and therapy for vascular disease have emerged over that time period, such as aspirin, statins, and angiotensin-converting-enzyme (ACE) inhibitors; these therapeutic developments, along with temporal changes in the disease—such as increasing prevalence of obesity—have well established effects on outcomes.^{32–34}

Placebo-controlled trials

Table 1 summarizes placebo-controlled trials of BP lowering in patients with hypertension and diabetes. The cohorts of patients with diabetes analyzed in early placebo-controlled, randomized trials provide important evidence supporting the dramatic benefit of reduction of systolic BP by ≥ 20 mmHg when baseline systolic BP was ≥ 170 mmHg.^{35,36} The systolic Hypertension in the Elderly Program (SHEP)³⁵ showed a 34% reduction in the rate of cardiovascular events and a 56% reduction in rates of coronary heart disease in elderly patients with diabetes over 5 years of follow-up. However, the systolic BP target in this trial was <160 mmHg for patients with BP >180 mmHg at baseline, or a reduction of 20 mmHg for those with baseline systolic BP between 160 mmHg and 179 mmHg. The Systolic Hypertension in Europe (Syst-Eur) trial,^{36,37} which was stopped early as a result of significant benefit in the active treatment group, confirmed a 62% reduction in risk of a cardiovascular event, and also observed a 69% reduction in the rate of strokes in patients with diabetes, over just 2 years of follow-up. However, target systolic BP in this trial was <150 mmHg. The action in Diabetes and vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) study,³⁸ which enrolled only patients with diabetes, was published almost a decade after SHEP and Syst-Eur. This trial demonstrated more modest, though significant reductions in cardiovascular risk associated with BP-lowering therapy, with a 14% reduction in all-cause mortality and 18% reduction in cardiovascular-related mortality after almost 5 years of follow-up. Of note, participants in ADVANCE had a mean baseline systolic BP of 145 mmHg, which was far below the baseline values observed in SHEP and Syst-Eur, and in fact was similar to or below the achieved systolic BP of patients in SHEP and Syst-Eur who received active treatment.^{35–37}

Intensive versus less-intensive BP goals

Table 2 summarizes studies of BP lowering with the use of intensive versus less-intensive therapy or BP goals in patients with hypertension and diabetes. The Hypertension Optimal

Treatment (HOT) study⁹ and the UK Prospective Diabetes study (UKPDS)¹⁰ were the first studies to randomly assign patients to less-intensive or more-intensive BP goals. The HOT study investigators randomly assigned patients to three different diastolic BP target groups (≤ 90 mmHg, ≤ 85 mmHg, and ≤ 80 mmHg). In the cohort of HOT participants with diabetes ($n = 1,501$), those in the ≤ 80 mmHg target group had a 51% reduced risk of cardiovascular events and 70% reduced risk of cardiovascular-related mortality compared with those in the ≤ 90 mmHg group after 4 years of follow-up.⁹ Notably, patients randomly assigned to the ≤ 80 mmHg target group achieved a mean BP of 144/81 mmHg, whereas those in the ≤ 90 mmHg target group achieved a mean BP of 148/85 mmHg. As in SHEP and the Syst-Eur trial, the baseline systolic BP of the HOT participants was very high, 170 mmHg, but the baseline diastolic BP was also very high, at 105 mmHg.⁹

The UKPDS investigators randomly assigned patients with diabetes to either 'tight BP control' ($<150/85$ mmHg) or 'less-tight BP control' ($<180/105$ mmHg).¹⁰ Patients in the $<150/85$ mmHg group had a mean baseline BP of 159/94 mmHg and achieved a mean BP of 144/82 mmHg, whereas those in the $<180/105$ mmHg group had a mean baseline BP of 160/94 mmHg and achieved a mean BP of 154/87 mmHg after more than 8 years of follow-up. Compared with the less-tight-control group, those in the tight-control group had a significant 44% reduction in risk of stroke ($P = 0.013$), a 32% reduction in risk of diabetes-related death ($P = 0.019$), and a 24% reduction in risk of diabetes-related end points ($P = 0.0046$).¹⁰ When the UKPDS investigators performed an additional 10-year follow-up of the patients, which included in-person visits and questionnaires but no attempt to intervene on BP, the benefits observed in the tight-control group at the first 8-year follow-up were no longer present.³⁹ Over the entire 20-year follow-up period, no difference in the rate of any diabetes-related end points, myocardial infarction (MI), microvascular disease, or all-cause mortality was observed between the tight-control and less-tight-control groups.³⁹

Investigators of the Appropriate Blood Pressure Control in Diabetes (ABCD) trial⁴⁰ randomly assigned patients with diabetes and high BP⁴¹ (mean baseline diastolic BP ≥ 90 mmHg) or who were normotensive⁴² (mean baseline diastolic BP 80–89 mmHg) to more-intensive and less-intensive diastolic BP goals. Patients with hypertension enrolled in the ABCD trial were randomly assigned to a diastolic BP goal of 75 mmHg (intense control) or 80–89 mmHg (less-intense control), whereas normotensive patients were randomly assigned to a 10 mmHg decrease in diastolic BP (intense control) or no intended change in diastolic BP (less-intense control). At 5 years, a significant 49% decrease in risk of all-cause mortality was observed in the population with hypertension in favor of intense BP control, although this risk was a secondary outcome. No difference in the primary outcome, a change in 24 h creatinine clearance, was observed. In the normotensive population, a significant 70% reduction in relative risk of stroke was seen, although this risk was also a secondary outcome, and only 17 strokes occurred during the 5 years of follow-up.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial^{11,31} investigators randomly assigned patients with hypertension and diabetes ($n = 4,733$) to antihypertensive therapy considered intensive (targeting a systolic BP of <120 mmHg) or standard (targeting a systolic BP of <140 mmHg). The risk of nonfatal MI, nonfatal stroke, or death from cardiovascular causes over a mean follow-up of 4.7 years was evaluated. ACCORD is the first large randomized trial that provides the opportunity to assess the effects of lower achieved systolic BP (<120 mmHg) in patients with diabetes. Patients randomly assigned to the intensive-therapy group achieved a mean BP of 119/64 mmHg whereas those in the standard-therapy group achieved a mean BP of 134/71 mmHg. No significant difference in risk of nonfatal MI or cardiovascular-related death was observed when comparing the intensive-therapy and standard-therapy groups. However, a significant 42% reduced risk of total stroke and 38% reduced risk of nonfatal stroke was seen, although the overall annual

stroke rate was very low (0.32% and 0.53% in the intensive-therapy and standard-therapy groups, respectively). Additionally, no information was provided regarding the level of functional disability resulting from the strokes, making it difficult to interpret the overall risk–benefit ratio for the stroke outcome. A significantly increased incidence of serious adverse events was also seen in the intensive-therapy group, including hypotension, bradycardia, and arrhythmia, all of which are known to be associated with poor outcomes. The ACCORD investigators concluded that their results provide no evidence that intensive BP control reduces the rate of a composite of major cardiovascular events.¹¹

Although it may be surprising that significant reductions in the rate of cardiovascular events were not observed in ACCORD, it is important to note that patients in ACCORD had lower systolic BP at baseline than that achieved in the intense-control groups of either HOT⁹ or UKPDS.¹⁰ This factor suggests that the benefit observed in the intense-control groups of HOT and UKPDS was likely to be based on reducing systolic BP from a mean ≥ 160 mmHg at baseline to 144 mmHg, and that the benefit of reducing systolic BP from an average baseline value of 139 mmHg to 119 mmHg, as was observed in ACCORD, is smaller. The normotensive population in ABCD is, among the patient groups studied in these trials, the one most similar to the ACCORD population, in factors such as BP, age, and percentage of patients with CVD at baseline. In both of these studies, a small, though significant, reduction in the risk of stroke was observed in the intense-therapy groups.

Analyses of achieved BP

Table 3 summarizes analyses of achieved systolic and diastolic BP following BP lowering in patients with hypertension and diabetes. The Irbesartan Diabetic Nephropathy Trial (IDNT)^{43,44} offers the opportunity to examine the effects of achieved BP on cardiovascular outcomes in a population of patients with hypertension and diabetes with nephropathy who were followed for 3 years. Progressively lower achieved systolic BP to 120 mmHg predicted a decrease in cardiovascular-related mortality and congestive heart failure, but not of MI. When patients were categorized according to achieved systolic BP of ≤ 120 mmHg ($n = 53$) or systolic BP > 120 mmHg ($n = 1,537$), a significant increase in relative risk of all-cause mortality as well as cardiovascular-related mortality was seen in the small group that achieved systolic BP of ≤ 120 mmHg.⁴⁴ Achieving diastolic BP < 85 mmHg was associated with a trend to increased all-cause mortality, a significant increase in risk of MI, but a decrease in risk of stroke. Although only 29% of IDNT participants had CVD at baseline, when categorized according to achieved systolic BP, a higher fraction of patients in the ≤ 120 mmHg group had a history of CVD or congestive heart failure at baseline compared with those in the > 120 mmHg group.⁴⁴

The International Verapamil SR/Trandolapril (INVEST) study⁴⁵ also offers the opportunity to assess the influence of achieved systolic BP on cardiovascular outcomes in a unique population of patients with hypertension and diabetes ($n = 6,400$), all of whom had documented coronary artery disease at baseline and were followed for 3 years. INVEST participants were categorized according to achievement of a systolic BP < 130 mmHg (tight control) or 130 mmHg to < 140 mmHg (usual control).¹² No difference was seen when comparing the tight-control and usual-control groups with regard to the rate of the primary outcome (first occurrence of all-cause death, nonfatal MI, or nonfatal stroke), nor was there any difference in the rates of nonfatal MI or nonfatal stroke when evaluated separately. However, a significant 8% increase was seen in the relative risk of all-cause mortality in the group with tight systolic control BP ($P = 0.04$). Extended follow-up of US participants in INVEST, using information from the National Death Index, revealed that over a total of 10 years patients in the tight systolic control BP group had a 15% excess risk of all-cause mortality compared with those in the usual systolic control BP group.¹² This excess risk was concentrated among those with systolic BP < 120 mmHg.

Microvascular benefit of BP lowering

Some of these studies also evaluated microvascular end points in patients with diabetes. In those receiving active treatment (perindopril and indapamide), investigators of ADVANCE found a significant reduction in the development of microalbuminuria ($P < 0.0001$), and a borderline significant reduction in the rate of new or worsening nephropathy ($P = 0.055$).³⁸ However, no difference between the active and control groups was found in the rate of new or worsening retinopathy, visual deterioration, or new or worsening neuropathy.³⁸ In UKPDS, patients in the tight-control group had a 34% reduction in risk of deterioration of retinopathy ($P = 0.0004$), and a 47% reduction in risk of deterioration in visual acuity by three lines according to the Early Treatment of Diabetic Retinopathy Study vision chart ($P = 0.004$),¹⁰ although these microvascular benefits were not sustained during UKPDS post-trial follow-up.³⁹ In those patients with normoalbuminuria or microalbuminuria enrolled in ABCD, BP lowering stabilized renal function in both groups; however, patients with overt albuminuria at baseline had a steady decline in creatinine clearance throughout the study regardless of BP reduction.⁴¹ In ACCORD, patients in the intensive-control group had significantly lower estimated glomerular filtration rate ($P < 0.001$), more cases of elevated serum creatinine ($P < 0.001$), and more cases of estimated glomerular filtration rate < 30 ml/min/1.73m² ($P < 0.001$), although significantly fewer cases of macroalbuminuria ($P = 0.009$).¹¹ In a substudy of ACCORD on retinopathy, intensive BP lowering was not associated with reduction in the rate of progression of diabetic retinopathy.⁴⁶

Hypertension treatment guidelines

Systolic and diastolic treatment goals for patients with diabetes, according to the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC), as well as the achieved systolic and diastolic BP levels in the studies reviewed here, are summarized in Figure 1. Before 1993, hypertension treatment guidelines did not specify different BP-lowering goals for those with or without diabetes, but rather recommended that all patients with hypertension be treated to a goal BP of $< 140/90$ mmHg.⁴⁷

In the fifth report of the JNC (JNC V),⁴ published in 1993, and in JNC VI published in 1997,⁵ the recommended BP goal for patients with diabetes was $< 130/85$ mmHg. Interestingly, no cited evidence-based data support this lower BP goal. It was not until 1998 that data from HOT9 and UKPDS10 were available, demonstrating benefit from lower BP goals in patients with diabetes. In 2002, the American Diabetes Association recommended that the BP treatment goal for patients with diabetes should be $< 130/80$ mmHg;²⁸ in 2003, JNC 7 confirmed this recommendation, although qualifying it by stating that “available data are somewhat sparse to justify the low target level of 130/80 mmHg”.⁶ In none of the studies conducted in patients with hypertension and diabetes before the publication of JNC 7 was a mean systolic BP goal of 130 mmHg actually achieved, although mean achieved diastolic BP was < 85 mmHg in all of the studies. In 2007, the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) confirmed the recommendation of $< 130/80$ mmHg in patients with diabetes in a joint publication.⁷ However, a reappraisal of the European guidelines on hypertension management in 2009 pointed out that evidence favoring a systolic BP target < 130 mmHg is almost nonexistent.⁴⁹ According to this reappraisal, the recommendation given to all patients with hypertension to lower systolic BP as much as possible below 140 mmHg seems realistic and prudent for patients with diabetes.⁴⁹ It was not until 2010, with the publication of ACCORD11 and INVEST,¹² that data became available to evaluate the effects of lowering systolic BP to levels first recommended almost two decades earlier. As postulated in the European reappraisal,⁴⁹ findings from ACCORD¹¹ and INVEST¹² do not support the recommendation of a systolic BP goal < 130 mmHg in patients with diabetes. In fact, the ACCORD

investigators write that “although it was not the intent of ACCORD to test the BP goal of 130 mmHg that was recommended in the JNC 7, it would be difficult to argue that such a target would be better than a target of 140 mmHg, since even a BP goal of 120 mmHg did not confer benefit”.¹¹ Although a reduction in the rate of fatal and nonfatal stroke was observed in the intensive-control group of ACCORD, the overall rate of stroke was low in this contemporary population of patients with diabetes. We concur with the ACCORD investigators in their opinion that a systolic BP target <130 mmHg is not justified by the currently available evidence, from ACCORD or the other studies reviewed here.

Does choice of medication matter?

A thorough discussion of the available data regarding the outcomes of treatment with various antihypertensive medications is beyond the scope of this Review. However, a meta-analysis of 27 randomized trials that included 33,395 patients with diabetes concluded that risk of total major cardiovascular events was reduced to a comparable extent with the use of BP-lowering regimens based on ACE inhibitors, calcium antagonists, angiotensin-receptor blockers, and diuretic- β -blocker combinations.⁵⁰ On the basis of the evidence showing substantial similarity of antihypertensive agents from various classes in preventing cardiovascular outcomes in patients with diabetes, the 2007 ESH/ESC guidelines recommend the use of any agent capable of effectively lowering BP in these patients.⁵¹ Since the publication of this large meta-analysis, data from the cohort of patients with diabetes ($n = 6,946$) of the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) study⁵² have been published. Results from this study indicate significantly reduced risk of cardiovascular events in those patients with diabetes who are treated with a combination of a calcium antagonist plus an ACE inhibitor compared with in those treated with a combination of a thiazide diuretic plus an ACE inhibitor.⁵³

A J-shaped curve relationship

The existence of a J-shaped curve reflecting the relationship between BP and cardiovascular outcomes has long been debated. Several reports have shown low diastolic BP to be associated with an increased risk of cardiovascular events, including mortality, in patients aged >55–60 years and in those taking anti hypertensives.^{54,55} A meta-analysis published in 1991, in which data from 13 studies were summarized, did not show a consistent J-shaped relationship between treated BP and risk of stroke; however, a consistent J-shaped relationship between the incidence of cardiac events and diastolic BP was observed.⁵⁶ Although this meta-analysis did not specifically focus on patients with diabetes, this group of patients was included in the studies, and adjustment for diabetes status was part of the analyses. The J-shaped relationship was more marked in individuals with existing CVD, although it was also observed in patients without CVD.⁵⁶ Data from HOT do not suggest presence of a J-shaped curve with regard to BP and cardiovascular outcomes,⁹ which has been the topic of some debate;^{57,58} however, only 6% of the overall HOT population had CVD at baseline, and lack of a J-shaped relationship might be a reflection of a population at low risk. Data from INVEST, which only enrolled patients with coronary artery disease, showed the relationship between BP and cardiovascular outcomes to be J-shaped in the whole population analyzed⁵⁹ and in the cohort with diabetes in particular.^{12,60} The IDNT investigators also observed a robust J-shaped relationship between every decrease of 10 mmHg in diastolic BP and increased risk of MI,⁴⁴ confirming the association between BP and risk observed in the meta-analysis published previously.⁵⁶

Data from observational epidemiology studies of patients with hypertension and diabetes add information regarding the association of BP and mortality. An analysis of 1,294 patients

with diabetes enrolled in the Botnia study⁶¹ showed that systolic and diastolic BP correlated negatively with mortality after adjustment for risk factors; this correlation was most pronounced in patients with a history of CVD. The Zwolle Outpatient Diabetes Project Integrating Available Care (ZODIAC-12) study⁶² demonstrated higher all-cause and cardiovascular-related mortality rates in very elderly patients (>75 years of age) with diabetes compared with younger patients with diabetes (60–75 years of age). Decreases of 10 mmHg in systolic or diastolic BP were associated with increases in mortality risk of 22% and 30%, respectively in the very elderly. However, in the group of younger ZODIAC-12 patients, no relationship was found between BP and mortality.⁶² After adjusting for confounders, the mortality risk increased by 16% and 24% for every 10 mmHg decrease in systolic and diastolic BP, respectively.

Baseline risk—important to consider?

Established guidelines for lowering BP in patients with diabetes are based on average results of trials evaluating the relative benefits of intensive BP control, and are not tailored to an individual's underlying CVD risk.⁶³ Guidelines implicitly assume all patients with diabetes to be at similarly high risk, and recommend that all patients in this group be treated aggressively; however, important, fundamental differences in patient characteristics exist and should be considered. SHEP³⁵ and Syst-Eur³⁷ required patients to undergo a placebo run-in period before randomization that lasted 2–8 weeks, and thus reported very high baseline BP in the untreated state. HOT⁹ did not require withdrawal of antihypertensive treatment before randomization, but only half of HOT participants were receiving treatment for hypertension at enrollment,⁶⁴ and baseline BP levels were similarly high. ACCORD¹¹ participants are the most contemporary population of patients enrolled in a hypertension intervention trial. The trial included patients with a 10-year history of diabetes, systolic and diastolic BP that were well controlled at baseline (139/78 mmHg), and a reasonably well controlled cholesterol profile of LDL 110 mg/dl, HDL 51 mg/dl in women and 42 mg/dl in men, and triglycerides 147 mg/dl, which represents a population at fairly low risk, despite the presence of diabetes. In fact, the ACCORD investigators state that the event rate in the less-intense-control group was 50% lower than expected, which they attribute to the frequent use of statins, as well as to patients with diabetes at higher risk who could possibly have been recruited in the ACCORD Lipid study instead.^{11,65}

Using Monte Carlo methods to simulate a treat-to-target strategy in a population with diabetes from the National Health and Nutrition Survey III, targets of 100 mg/dl LDL and 130/80 mmHg BP were evaluated.⁶³ Up to five titrations of statin therapy and eight titrations of antihypertensive therapy were investigated, and treatment-associated adverse effects and risks and burdens of polypharmacy were incorporated to simulate health outcomes. Overall, the simulation revealed that treating to targets resulted in gains of 1.5 and 1.35 quality-adjusted life-years of lifetime treatment-related benefit for LDL and BP, respectively; however, most of the benefit was limited to the first few steps of medication intensification or to tight control for the limited group of patients at very high risk. Importantly, there was treatment-related disutility where intensification beyond the first step (in the case of LDL control) or third step (in the case of BP control) resulted in either limited benefit or net harm for patients at below-average risk. This finding led the investigators to conclude that the benefits and harms of aggressive risk factor modification vary widely across the population of individuals with diabetes in the USA. Therefore, depending on a patient's underlying risk of CVD, a personalized approach could maximize a patient's net benefit from treatment.⁶³ Although the mathematical models employed in this simulation contain assumptions and approaches that require validation,²⁶ the message is profound in an era in which the prevalence of diabetes is expected to reach 29 million in the USA alone by 2050.⁶⁶

Conclusions

On the basis of available evidence from placebo-controlled trials, randomized trials, and achieved BP analyses, the target BP levels recommended in current guidelines (<130/80 mmHg) are not supported for the prevention of macrovascular outcomes in patients with diabetes. Consideration should be given not only to an individual's current BP level, but also to their underlying level of overall risk before assigning a BP treatment target. Current data support BP lowering to <140 mmHg in patients with and without diabetes. Additionally, other risk factors should be managed in each patient as appropriate, including smoking cessation, weight loss, and cholesterol management, to reduce overall long-term cardiovascular risk.

Review criteria

A search for original articles, reviews, and meta-analyses that focused on hypertension prevalence and treatment outcomes and diabetes was performed in MEDLINE and PubMed. The search terms used were “hypertension”, “diabetes”, “cardiovascular risk”, and “guidelines”. All papers identified were English-language, full-text papers and no time limits were set. The reference lists of identified articles were also searched for additional material.

References

1. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 1993;16:434–444. [PubMed: 8432214]
2. Sowers JR, Epstein M, Frohlich ED. Diabetes, hypertension, and cardiovascular disease: an update. *Hypertension* 2001;37:1053–1059. [PubMed: 11304502]
3. The 1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. *Arch. Intern. Med* 1984;144:1045–1057. [No authors listed]. [PubMed: 6143542]
4. The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). *Arch. Intern. Med* 1993;153:154–183. [No authors listed]. [PubMed: 8422206]
5. 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. [No authors listed]. [PubMed: 9385294]
6. Chobanian AV, 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. [PubMed: 12748199]
7. Mancia G, 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;28:1462–1536. [PubMed: 17562668]
8. American Diabetes Association. Treatment of hypertension in adults with diabetes. *Diabetes Care* 2002;25:199–201. [PubMed: 11772916]
9. Hansson L, 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;351:1755–1762. [PubMed: 9635947]
10. 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. [No authors listed]. [PubMed: 9732337]
11. Cushman WC, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N. Engl. J. Med* 2010;362:1575–1585. [PubMed: 20228401]

12. Cooper-DeHoff RM, et al. Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. *JAMA* 2010;304:61–68. [PubMed: 20606150]
13. International Diabetes Federation. About diabetes. 2010. [online], <http://www.idf.org/about-diabetes>
14. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. *Diabetes Care* 2004;27:1047–1053. [PubMed: 15111519]
15. Kannel WB, Wilson PW, Zhang TJ. The epidemiology of impaired glucose tolerance and hypertension. *Am. Heart J* 1991;121:1268–1273. [PubMed: 2008855]
16. Klein R, Klein BE, Lee KE, Cruickshanks KJ, Moss SE. The incidence of hypertension in insulin-dependent diabetes. *Arch. Intern. Med* 1996;156:622–627. [PubMed: 8629873]
17. Fryar, CD.; Hirsch, R.; Eberhardt, MS.; Yoon, SS.; Wright, JD. Hypertension, high serum total cholesterol, and diabetes: racial and ethnic prevalence differences in U. S. adults, 1999–2006. 2010. [online], <http://www.cdc.gov/nchs/data/databriefs/db36.pdf>
18. Mancia G. The association of hypertension and diabetes: prevalence, cardiovascular risk and protection by blood pressure reduction. *Acta Diabetol* 2005;42 Suppl. 1:S17–S25. [PubMed: 15868115]
19. Creager MA, Lüscher TF, Cosentino F, Beckman JA. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: Part I. *Circulation* 2003;108:1527–1532. [PubMed: 14504252]
20. Haffner SM, Lehto S, Rönnekaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N. Engl. J. Med* 1998;339:229–234. [PubMed: 9673301]
21. Stern MP. Diabetes and cardiovascular disease. The “common soil” hypothesis. *Diabetes* 1995;44:369–374. [PubMed: 7698502]
22. Redon J, et al. Mechanisms of hypertension in the cardiometabolic syndrome. *J. Hypertens* 2009;27:441–451. [PubMed: 19262221]
23. Cooper SA, et al. Renin-angiotensin-aldosterone system and oxidative stress in cardiovascular insulin resistance. *Am. J. Physiol. Heart Circ. Physiol* 2007;293:H2009–H2023. [PubMed: 17586614]
24. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002;360:1903–1913. [PubMed: 12493255]
25. Adler AI, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ* 2000;321:412–419. [PubMed: 10938049]
26. Avins AL. When clinical practice guidelines meet the black box. *Arch. Intern. Med* 2010;170:1013–1014. [PubMed: 20585064]
27. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Heart Outcomes Prevention Evaluation Study Investigators. *Lancet* 2000;355:253–259. [No authors listed]. [PubMed: 10675071]
28. American Diabetes Association. Standards of medical care for patients with diabetes mellitus. *Diabetes Care* 2002;25:213–229. [PubMed: 11772918]
29. American Diabetes Association. Standards of medical care in diabetes—2010. *Diabetes Care* 2010;33 Suppl. 1:S11–S61. [PubMed: 20042772]
30. Chobanian AV, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003;42:1206–1252. [PubMed: 14656957]
31. Cushman WC, et al. Rationale and design for the blood pressure intervention of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Am. J. Cardiol* 2007;99:44i–55i.
32. Yusuf S, et al. 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. [PubMed: 10639539]

33. Braunwald E, et al. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N. Engl. J. Med* 2004;351:2058–2068. [PubMed: 15531767]
34. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7–22. [PubMed: 12114036]
35. Curb JD, et al. Effect of diuretic-based antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated systolic hypertension. Systolic Hypertension in the Elderly Program Cooperative Research Group. *JAMA* 1996;276:1886–1892. [PubMed: 8968014]
36. Staessen JA, et al. Randomised double-blind comparison of placebo and active treatment for older patients with isolated systolic hypertension. The Systolic Hypertension in Europe (Syst-Eur) Trial Investigators. *Lancet* 1997;350:757–764. [PubMed: 9297994]
37. Tuomilehto J, et al. Effects of calcium-channel blockade in older patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators. *N. Engl. J. Med* 1999;340:677–684. [PubMed: 10053176]
38. Patel A, et al. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *Lancet* 2007;370:829–840. [PubMed: 17765963]
39. Holman RR, Paul SK, Bethel MA, Neil HA, Matthews DR. Long-term follow-up after tight control of blood pressure in type 2 diabetes. *N. Engl. J. Med* 2008;359:1565–1576. [PubMed: 18784091]
40. Schrier RW, Estacio RO, Jeffers B. Appropriate Blood Pressure Control in NIDDM (ABCD) Trial. *Diabetologia* 1996;39:1646–1654. [PubMed: 8960857]
41. Estacio RO, et al. The effect of nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-dependent diabetes and hypertension. *N. Engl. J. Med* 1998;338:645–652. [PubMed: 9486993]
42. 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;61:1086–1097. [PubMed: 11849464]
43. Lewis EJ, et al. 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. [PubMed: 11565517]
44. Berl T, et al. Impact of achieved blood pressure on cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial. *J. Am. Soc. Nephrol* 2005;16:2170–2179. [PubMed: 15930097]
45. Pepine CJ, et al. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International verapamil-Trandolapril Study (INVEST): a randomized controlled trial. *JAMA* 2003;290:2805–2816. [PubMed: 14657064]
46. Chew EY, et al. Effects of medical therapies on retinopathy progression in type 2 diabetes. *N. Engl. J. Med* 2010;363:233–244. [PubMed: 20587587]
47. The 1988 report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. *Arch. Intern. Med* 1988;148:1023–1038. [No authors listed]. [PubMed: 3365073]
48. American Diabetes Association. Diabetic nephropathy. *Diabetes Care* 2002;25 Suppl. 1:S85–S88.
49. Mancia G, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J. Hypertens* 2009;27:2121–2158. [PubMed: 19838131]
50. Turnbull F, et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. *Arch. Intern. Med* 2005;165:1410–1419. [PubMed: 15983291]
51. Mancia G, et al. 2007 ESH-ESC Practice Guidelines for the Management of Arterial Hypertension: ESH-ESC Task Force on the Management of Arterial Hypertension. *J. Hypertens* 2007;25:1751–1762. [PubMed: 17762635]
52. Jamerson K, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N. Engl. J. Med* 2008;359:2417–2428. [PubMed: 19052124]
53. Weber MA, et al. Cardiovascular events during differing hypertension therapies in patients with diabetes. *J. Am. Coll. Cardiol* 2010;56:77–85. [PubMed: 20620720]

54. Cruickshank JM, Thorp JM, Zacharias FJ. Benefits and potential harm of lowering high blood pressure. *Lancet* 1987;1:581–584. [PubMed: 2881129]
55. Alderman MH, Ooi WL, Madhavan S, Cohen H. Treatment-induced blood pressure reduction and the risk of myocardial infarction. *JAMA* 1989;262:920–924. [PubMed: 2754792]
56. 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;265:489–495. [PubMed: 1824642]
57. Grossman E. Does the ‘J-curve’ still hold in the post ‘HOT’ era? *J. Hum. Hypertens* 1998;12:729–730. [PubMed: 9844940]
58. Ibsen H. Intensive blood pressure lowering warranted. Results of the HOT study: an epitaph for the J-curve concept in hypertension. *J. Hum. Hypertens* 1998;12:731–732. [PubMed: 9844941]
59. Messerli FH, 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. [PubMed: 16785477]
60. Bakris GL, et al. Clinical outcomes in the diabetes cohort of the International Verapamil SR-Trandolapril study. *Hypertension* 2004;44:637–642. [PubMed: 15381674]
61. Rönnback M, et al. Complex relationship between blood pressure and mortality in type 2 diabetic patients: a follow-up of the Botnia Study. *Hypertension* 2006;47:168–173. [PubMed: 16380522]
62. van Hateren KJ, et al. Lower blood pressure associated with higher mortality in elderly diabetic patients (ZODIAC-12). *Age Ageing* 2010;39:603–609. [PubMed: 20621928]
63. Timbie JW, Hayward RA, Vijan S. Variation in the net benefit of aggressive cardiovascular risk factor control across the US population of patients with diabetes mellitus. *Arch. Intern. Med* 2010;170:1037–1044. [PubMed: 20585069]
64. Hansson L, Zanchetti A. The Hypertension Optimal Treatment (HOT) Study—patient characteristics: randomization, risk profiles, and early blood pressure results. *Blood Press* 1994;3:322–327. [PubMed: 7866597]
65. Ginsberg HN, et al. Effects of combination lipid therapy in type 2 diabetes mellitus. *N. Engl. J. Med* 2010;362:1563–1574. [PubMed: 20228404]
66. Boyle JP, et al. Projection of diabetes burden through 2050: impact of changing demography and disease prevalence in the U.S. *Diabetes Care* 2001;24:1936–1940. [PubMed: 11679460]

Figure 1.

Systolic and diastolic BP treatment goals for patients with diabetes. Systolic (red line) and diastolic (blue line) treatment goals for patients with diabetes according to guidelines from the JNC, as well as the achieved systolic (circles) and diastolic (squares) BP levels in the studies reviewed in this article, according to publication year. The vertical lines represent the time periods the guidelines were in use. Abbreviations: BP, blood pressure; JNC, Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.

Table 1
Studies of BP lowering in patients with hypertension and diabetes: placebo-controlled trials

Study (publication year)	Mean follow-up (years)	Patients with diabetes (n)	Age at baseline (years)	CVD at baseline (%)	Mean baseline systolic/diastolic BP (mmHg)		Achieved systolic/diastolic BP at the end of study (mmHg)		Outcome and change in relative risk
					Active treatment	Placebo	Active treatment	Placebo	
SHEP (1996) ³⁵	5	583	71	5 (history of MI)	170/77	170/75	146/68 ³¹	155/72 ³¹	CVD events ↓34% CHD events ↓56%
Syst-Eur (1997) ³⁷	2	492	70*	35	175/85	175/85	153/78	162/82	Stroke ↓69% Cardiovascular events ↓62%
ADVANCE (2007) ³⁸	4.3	11,140	66	32	145/81	145/81	136/73	140/73	All-cause mortality ↓14% Cardiovascular-related mortality ↓18%

* Overall Syst-Eur population.

Abbreviations: BP, blood pressure; CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction.

Table 2
Studies of BP lowering in patients with hypertension and diabetes: intensive versus less-intensive therapy or BP goals

Study (publication year)	Mean follow-up (years)	Patients with diabetes (n)	Age at baseline (years)	CVD at baseline (%)	Mean baseline systolic/diastolic BP (mmHg)		Achieved systolic/diastolic BP at the end of study (mmHg)		Outcome and change in relative risk
					More intensive	less intensive	More intensive	less intensive	
HOT (1998) ⁹	3.8	1,501	62	~6*	170/105*	170/105*	144/81	148/85	Cardiovascular events ↓51% Cardiovascular-related mortality ↓70%
UKPDS (1998) ¹⁰	8.4	1,148	56	NA	159/94	160/94	144/82	154/87	Diabetes-related death ↓32% Stroke ↓44% Diabetes-related end point ↓24%
ABCD Hypertensive (1998) ⁴¹	5.3	470	58	53	156/98	154/98	132/78	138/86	All-cause mortality ↓49%
ABCD Normotensive (2002) ⁴²	5.3	480	59	24	135/84	137/84	128/75	137/81	CVD ↓70% (Total strokes n = 17)
ACCORD (2010) ¹¹	4.7	4,733	62	30	139/76	139/76	119/64	134/71	Any stroke ↓42% Nonfatal stroke ↓38% (Total strokes n = 98)

* Overall HOT population.

Abbreviations: BP, blood pressure; CVD, cardiovascular disease; NA, not available.

Table 3

Studies of BP lowering in patients with hypertension and diabetes: analyses of achieved systolic and diastolic BP

Study (publication year)	Mean follow-up (years)	Patients with diabetes (n)	Age at baseline (years)	CVD at baseline (%)	Mean baseline systolic/diastolic BP (mmHg)		Achieved systolic/diastolic BP at the end of study (mmHg)		Outcome and change in relative risk
					Tight control	Usual control	Tight control	Usual control	
IDNT (2005) ^{43,44}	3.0	1,590	59	29	≤120 140/84	>120 159/87	≤120, n = 53 (3%)	>120, n = 1,537 (97%)	All-cause mortality ↑133% Cardiovascular-related mortality ↑216%
INVEST (2010) ¹²	2.7	6,400	66	100	<130 144/85	130–<140 149/85	<130 123/74	130–<140 133/77	All-cause mortality ↑8%

Abbreviations: BP, blood pressure; CVD, cardiovascular disease.