The effects of aggressive blood pressure (BP) management on the risks of coronary heart disease (CHD) and other vascular outcomes among individuals with type 2 diabetes mellitus (T2DM) has been a matter of intense debate recently, with the results of large-scale clinical trials leading to variable interpretation. This chapter reviews the epidemiologic associations between BP and CHD in diabetes and the efficacy of BP lowering on CHD outcomes, focusing on evidence about the direct and off-target effects of different classes of BP-lowering drugs, the results of relevant clinical trials evaluating the relative merits of intensive BP management, and the potential role of new and emerging clinical interventions. Finally, these will be placed within the context of effects of BP lowering on other clinical outcomes, the role of absolute risk assessment for guiding BP management, and a global perspective of current levels of success in achieving adequate BP control in patients with T2DM.

### Epidemiologic Associations Between Blood Pressure and Coronary Heart Disease in People with Type 2 Diabetes Mellitus

On average, systolic BP (SBP) and diastolic BP (DBP) are consistently higher among individuals with T2DM compared with those without T2DM. Nonoptimal BP is a well-established risk factor for people with and without diabetes. In general populations, there is clear log-linear association between both SBP and DBP and CHD, evident within any adult age group. This association appears continuous across the range of BP, down to at least SBP of 115 mm Hg and DBP of 75 mm Hg, such that for adults aged 40 to 89 years, a 20-mm Hg difference in SBP is associated with an approximate 45% difference in risk of CHD. In 386,307 people with diabetes included in the Asia Pacific Cohort Studies Collaboration, a similar continuous association was observed for both Asian and non-Asian populations. Among those with diabetes, a 10-mm Hg lower level of SBP was associated with an 18% lower level of CHD, which was not statistically different from the 23% lower level of CHD observed in people without diabetes (Fig. 14-1).

Further data relating to epidemiologic associations have been derived from observational analyses of clinical trial populations. The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that a higher level of average SBP within a range from below 120 mm Hg to above 160 mm Hg was associated with a greater risk of myocardial infarction (MI) of approximately 12%/10-mm Hg increment. More recently, observational subgroup analyses of the International Verapamil SR Trandolapril Study (INVEST) suggested a possible J-curve relationship with a threshold on-treatment SBP level of 125 to 130 mm Hg in diabetic patients with established stable coronary artery disease with respect to all-cause mortality. By and large, however, the epidemiologic data have formed a credible basis for the hypothesis that benefits of BP-lowering therapy might accrue to individuals with T2DM down to levels of SBP well below currently accepted thresholds for the diagnosis of hypertension.

Although these epidemiologic data provide a basis for expecting a reduction in CHD events from interventions that reduce BP in people with T2DM, the results from well-designed and appropriately powered randomized trials should inform recommendations for clinical and public health practice. Such trials have been conducted, evaluating both lifestyle interventions and drugs, and are summarized in the following sections.

### Efficacy of Lifestyle Interventions on Blood Pressure Levels and Coronary Heart Disease Risk in Patients with Type 2 Diabetes Mellitus

Initial attempts at BP reduction through lifestyle modification are emphasized in guidelines for the management of hypertension worldwide in individuals with or without diabetes. These have principally focused on increasing physical activity, reducing body weight and/or adiposity,
MANAGEMENT OF CORONARY HEART DISEASE RISK AND DISEASE IN PATIENTS WITH DIABETES

Diabetes: 1.18 per 10 mm Hg (1.09-1.27); $P_{\text{trend}} < 0.001$

No diabetes: 1.23 per 10 mm Hg (1.19-1.26); $P_{\text{trend}} < 0.001$

**FIGURE 14-1** Association between usual systolic blood pressure (SBP) and coronary heart disease (CHD) events by diabetes status in the Asia Pacific Cohort Studies Collaboration. For each association, the hazard ratio (95% confidence interval [CI]) for a 10-mm Hg higher level of systolic blood pressure (SBP) compared with SBP 120 mm Hg as reference and the $P$ value for linear trend are indicated (upper value for those without diabetes [red]; lower value for those with diabetes [blue]). Usual = baseline values corrected for regression dilution bias (using repeated measures). (Reproduced with permission from Asia Pacific Cohort Studies Collaboration; Kangne AP, Patel A, Bazi F, et al: Systolic blood pressure, diabetes and the risk of cardiovascular diseases in the Asia-Pacific region, J Hypertens 25:1205-1213, 2007.)

and performing dietary modification, including salt restriction. Although a number of studies have evaluated the effects of lifestyle interventions on diabetes incidence, the Look AHEAD (Action for Health in Diabetes) trial examined the sustained effects of an intensive lifestyle intervention in 5145 overweight or obese adults with T2DM. Over an average of 4 years and compared with a diabetes support and education control group, intensive lifestyle intervention was associated with significant improvements for a number of vascular risk factors, including significant net reductions in SBP (−2.33 mm Hg) and DBP (−0.44 mm Hg). The intervention evaluated and targeted both physical activity and diet, and separate effects of individual components of the lifestyle intervention on BP cannot be estimated. Inferences about how this might translate to reductions in CHD risk currently can be based only on projections from observational studies comparing BP level or changes in BP level with clinical outcomes. Published data from Look AHEAD to date are the result of a prespecified interim comparison of effects on risk factors only, in a trial designed to evaluate the effects of the intensive lifestyle intervention on clinical outcomes after an average of 13.5 years of follow-up. (See also Chapters 5 and 12.)

Although not restricted to people with diabetes, the Dietary Approaches to Stop Hypertension (DASH) trials provide some indication of the likely effects of certain diets on BP. Allocation to the DASH diet (rich in fruits, vegetables, and low-fat dairy foods and with reduced saturated and total fat) in 459 adults over an 8-week intervention period was associated with significant reductions in SBP and DBP of 5.5 mm Hg and 3.0 mm Hg, respectively, compared with a “typical” control diet. In the subsequent DASH-sodium trial, participants were randomly assigned different levels of sodium intake, within DASH or control diets. The effects of different levels of sodium intake in addition to the DASH diet were evaluated. Greatest benefits were observed with a low-sodium DASH diet, which compared with a control high-sodium diet, reduced SBP by 11.5 mm Hg in participants with hypertension and 7.1 mm Hg in those without a diagnosis of hypertension. With small numbers of participants, analysis in the subgroup with diabetes was not possible. A recent updated Cochrane Review of 167 studies concluded that dietary sodium reduction over at least 4 weeks resulted in significant reductions in BP, with greater effects among people with hypertension versus those considered normotensive and possibly in non-Caucasians versus Caucasians. Although there are some dissenting views, many believe the existing evidence adequately favors common recommendations for individual salt intake to be limited to less than 5 g/day, particularly in individuals with hypertension, although a Cochrane review of individual patient strategies to reduce salt intake suggest that more effective approaches to achieve such reductions are urgently required.

**EFFICACY AND SAFETY OF BLOOD PRESSURE-LOWERING DRUGS ON CORONARY HEART DISEASE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS**

Multiple guidelines for pharmacologic lowering of BP in patients with T2DM exist worldwide, with some major examples summarized in Table 14-1. Some of the evidence on which these recommendations are based is outlined here.

**Overall Efficacy—Placebo-Controlled Trials**

The most comprehensive overview of the effects of BP-lowering medications on vascular outcomes is provided by the Blood Pressure Lowering Treatment Trialists’ Collaboration (BPLTTC). There have been two cycles of prospectively defined group and individual participant data meta-analyses conducted through this collaboration, most recently in 2003. The systematic reviews of placebo-controlled trials in the second cycle included nine studies and 25,731 individuals. The researchers concluded that, compared with placebo, angiotensin-converting enzyme (ACE) inhibitors and calcium antagonists each reduced the risk of CHD by approximately 20% in general populations, with much greater precision around the estimate for ACE inhibitors. Further analyses of placebo-controlled comparisons among individuals with and without diabetes did not find any evidence of statistical heterogeneity for effects on CHD.

Since the second cycle of the BPLTTC was published, the largest-ever-conducted placebo-controlled trial of BP lowering among individuals with T2DM was completed. The Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial was a randomized study of 11,140 individuals with T2DM from 214 collaborating centers in 20 countries from Asia, Australasia, Europe, and North America. Participants with known cardiovascular or microvascular disease or with at least one major risk factor for cardiovascular disease and any initial level of BP and glycosylated hemoglobin were randomly assigned, in a factorial design, to a fixed combination of the ACE inhibitor perindopril and the thiazide diuretic indapamide (4/1.25 mg) or matching placebo,
and to intensive glucose control or standard guideline-based glucose control. The two primary outcomes were a composite of major cardiovascular (nonfatal acute MI, nonfatal stroke and cardiovascular death) and major microvascular events (new or worsening nephropathy and microvascular eye disease), analyzed jointly and separately. The average duration of follow-up was 4.3 years for the BP-lowering intervention. It is important to note that in the BP treatment comparison aspect of the study, ADVANCE was testing the effects of a strategy of routinely administering BP-lowering therapy to individuals with diabetes at high risk for a cardiovascular event, regardless of initial BP level. Specifically, this trial was not designed to evaluate different target BP levels.

The mean BP of participants at study baseline in ADVANCE was 145/81 mm Hg, with over 40% recording a BP event, regardless of initial BP level. Specifically, this trial was not designed to evaluate different target BP levels.

The mean BP of participants at study baseline in ADVANCE was 145/81 mm Hg, with over 40% recording a BP event, regardless of initial BP level. Specifically, this trial was not designed to evaluate different target BP levels.
and 140.3/77.0 mm Hg in the placebo group. Active treatment reduced the risk of the combined composite primary outcome of major microvascular and macrovascular (cardiovascular) events by 9% (95% confidence interval [CI] 0% to 17%, P = 0.043). Considered individually, the effect on major macrovascular events was of similar magnitude but not statistically significant between the randomized groups. Among those on active treatment, there was a 14% (2%-25%; P = 0.025) reduction in all-cause mortality, driven by an 18% (2%-32%; P = 0.027) reduction in cardiovascular mortality. In addition, there was a 14% (2%-24%; P = 0.020) relative risk reduction in CHD events (defined as death caused by CHD, nonfatal MI, silent MI, coronary revascularization, or hospital admission for unstable angina), all of which were prespecified secondary outcomes. There was no evidence of heterogeneity in treatment effect in subgroups of participants defined by key baseline characteristics including age, sex history of cardiovascular disease, and background use of BP-lowering therapy. In particular, the effects of the combination perindopril and indapamide treatment were similar across a range of initial BP levels and regardless of use of other concomitant preventive therapies (including other BP-lowering agents, statins, and aspirin). The results of this BP intervention aspect of the ADVANCE study point to the potential benefits of an alternative strategy for delivery of BP-lowering treatment, as opposed to traditional threshold and target-driven strategies in which therapy is limited to patients with arbitrarily defined “hypertension” and therefore potentially denied to a broader range of high-risk individuals with apparently “normal” BP levels.

### Comparative Efficacy of Blood Pressure-Lowering Drugs

There has been considerable debate about the potential existence of BP-independent beneficial effects of various classes of drugs used to lower BP in a broad group of high-risk patients, including those with diabetes and with respect to different vascular beds. This possibility of differential class effects was explored extensively in the second cycle of BPLTTC, which analyzed data from 29 trials, specifically focused on the magnitude of benefits on clinical outcomes produced by different regimens of BP-lowering therapy, and attempted to relate any observed differences to effects on BP through meta-regression. In general populations and based on head-to-head comparisons, there were no significant differences among regimens based on ACE inhibitors, calcium channel blockers diuretics, or beta blockers. Overall, the efficacy of treatment correlated well with the degree of BP reduction achieved, although separate meta-regression has suggested modest additional BP lowering–independent effects of ACE inhibitors on CHD risk. This question has also been explored through comparisons of individuals with and without diabetes, using data from 29 randomized trials (33,395 individuals with diabetes and 125,314 participants without diabetes). Comparisons among individuals with diabetes showed point estimates favoring ACE inhibitors versus either diuretics or beta blockers, or versus calcium channel blockers for the prevention of CHD events; however, these were not statistically significant. There was no evidence of differential effects on CHD outcomes when calcium channel blockers were compared with diuretics or beta blockers. For all outcomes, there was no clear evidence of heterogeneity in the estimates of comparative treatment effects on CHD between individuals with and without diabetes (Fig. 14-8).

![Figure 14-2](https://clinicalkey.com/)

**FIGURE 14-2 Effects of BP-lowering medication classes versus placebo on the risk of CHD in patients with and without diabetes mellitus.** Asterisk indicates the overall mean BP difference (systolic and diastolic) during follow-up in the actively treated or first-listed group compared with the control or second-listed group, calculated by weighting the difference observed in each contributing trial by the number of individuals in the trial. Negative values indicate lower mean follow-up BP levels in first-listed treatment groups than in second-listed groups. ACE = Angiotensin converting enzyme; CCB = calcium channel blocker; CI = confidence interval; RRR = relative risk ratio. (Modified from Turnbull F, Neal B, Algert C, 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 165:1410-1419, 2005.)
The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) included 25,620 patients at increased risk for cardiovascular disease. The trial involved 19,257 participants, 27% of whom had diabetes at study entry. The point estimate of treatment effect favored the amlopidine-perindopril combination for the primary outcome, but this was not statistically significant. However, there were significant reductions in all secondary outcomes associated with the amlopidine-perindopril combination, ranging from a relative risk reduction of 11% to 24%, and including all-cause mortality (which led to early termination of the trial), all coronary events, and non-fatal MI and fatal CHD. However, it should be noted that despite a goal of achieving similar BP levels in both treatment arms, the amlopidine-based regimen was associated with a significant 2.7/1.9 mm Hg lower BP over the duration of follow-up. There was no evidence of heterogeneity of the treatment effect by the presence or absence of diabetes, evaluated on the basis of total cardiovascular outcomes.

The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) included 25,620 patients at increased risk for cardiovascular disease. Approximately 40% of study participants had diabetes at study entry. Patients were randomized to ramipril alone, to telmisartan alone, or to both drugs. The mean BP level at study entry was 142/82 mm Hg. Over the duration of follow-up, BP was 2.4/1.4 mm Hg lower in the combination therapy group compared with the ramipril-alone group. The incidence of the primary outcome (cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalized heart failure) did not differ between the ramipril-alone group and each of the other randomized groups. As expected, participants allocated to telmisartan alone experienced less cough and angioedema than those who were randomized to ramipril. However, symptoms of hypotension occurred more frequently in the telmisartan group (2.7%) and in the combination group (4.8%) compared with the ramipril-alone group (1.7%). Renal dysfunction was observed most often in the combination group. It is important to note that there was no heterogeneity in treatment effects by diabetes status for the primary outcome. In summary, the results of ONTARGET confirmed comparable efficacy of the ACE inhibitor and the ARB, but provided no evidence of additional benefit from combination therapy.

The Avoiding Cardiovascular Events through Combination Therapy to Patients Living with Systolic Hypertension (ACCOMPLISH) trial is also relevant to populations with diabetes. Approximately 60% of the 11,506 high-risk patients with hypertension included in this study had an additional diagnosis of diabetes at study entry. Patients were randomly allocated to receive one of two combination drug regimens—the ACE inhibitor benazepril plus the calcium channel blocker amlodipine, or benazepril with the diuretic hydrochlorothiazide (HCT). The mean baseline BP level was 145/80 mm Hg. Over the duration of follow-up, a 0.9/1.1 mm Hg lower BP was observed in the benazepril-amlodipine group compared with the benazepril-HCT group. This study was stopped prematurely after a mean follow-up period of 3 years because of an observed statistically significant 20% reduction in the primary outcome (cardiovascular death, nonfatal MI, nonfatal stroke, hospitalization for angina, resuscitation after cardiac arrest, and coronary revascularization) in the benazepril-amlodipine group compared with the benazepril-HCT group. As with ONTARGET, there was no

### Table 14-3

<table>
<thead>
<tr>
<th>Trials, No.</th>
<th>Events/participants, No.</th>
<th>ΔBP, mm Hg*</th>
<th>Favors first listed</th>
<th>Favors second listed</th>
<th>RRR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitor versus D/BB</td>
<td>Diabetes 5 402/4385 623/6614</td>
<td>2.2/0.3</td>
<td>0.83 (0.62–1.12)</td>
<td>0.98 (0.88–1.09)</td>
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</tr>
<tr>
<td>No diabetes 4 770/15810 1035/19744</td>
<td>1.5/0.2</td>
<td>0.96 (0.87–1.07)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Overall (P homog = 0.33)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CCB versus D/BB</td>
<td>Diabetes 8 431/6276 638/8550</td>
<td>0.7/−0.8</td>
<td>1.00 (0.99–1.13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes 8 935/23813 1175/27928</td>
<td>1.1/−0.4</td>
<td>1.01 (0.93–1.10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (P homog = 0.86)</td>
<td></td>
<td></td>
<td>1.01 (0.94–1.08)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACE inhibitor versus CCB</td>
<td>Diabetes 5 358/4101 407/4222</td>
<td>1.6/1.2</td>
<td>0.78 (0.51–1.12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes 3 549/8897 541/8536</td>
<td>1.3/0.9</td>
<td>0.98 (0.84–1.15)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (P homog = 0.22)</td>
<td></td>
<td></td>
<td>0.83 (0.65–1.05)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*ΔBP indicates the mean difference in BP between the groups.
evidence of heterogeneity based on baseline diagnosis of diabetes. Although early concerns had been expressed about potential underestimation of the BP difference between treatment arms using on-trial measurements, subsequent results of 24-hour ambulatory BP monitoring in a subset of 573 participants did not show any significant differences. 26

By and large, current hypertension and diabetes management guidelines worldwide acknowledge that achieving BP reduction is more pressing than decisions about which class of drug should be used, particularly given that two or more agents are frequently required in patients with diabetes. 8–13 In general, use of a regimen that includes an ACE-inhibitor or an angiotensin receptor blocker (ARB) is recommended, particularly in the presence of albuminuria. Although thiazide or thiazide-like diuretics as well as beta blockers have been associated with adverse effects on glucose homeostasis, the clinical relevance of this is doubtful and it does not preclude the use of these drugs in people with T2DM. Indeed, the indications for use of beta blockers in patients with existing CHD or systolic heart failure (particularly vasodilating beta blockers, such as carvedilol and nebivolol, which may also have more favorable metabolic effects than older beta blockers) 29,30 and thiazide or thiazide-like diuretics in those with cerebrovascular disease are compelling. 31,32 For much of the world, affordability of different classes of BP-lowering drugs is also a key issue that must be considered in choice of antihypertensive therapy.

**More versus Less Blood Pressure Lowering and Target Blood Pressure Levels**

Although acknowledging limitations of available randomized evidence, most guidelines worldwide currently recommend more aggressive management of hypertension (mostly, a target of 130/80 mm Hg or lower) among people with diabetes compared with those without diabetes. 8–15 In 1998, the UKPDS was the landmark trial that first compared more intensive BP lowering (with an ACE inhibitor or a beta blocker–based regimen) with less intensive control among newly diagnosed patients with T2DM and hypertension. The target BP levels for the randomized groups were below 150/85 mm Hg versus below 180/105 mm Hg, respectively. Achieved mean final BP levels were 144/82 mm Hg in the more intensive BP-lowering arm and 154/87 mm Hg in the less intensive BP-lowering arm. Compared with less tight control, more intensive BP lowering resulted in significant reductions in all “diabetes-related endpoints,” as well as cerebrovascular events and microvascular disease. 33 For the secondary outcome of MI (fatal or nonfatal MI or sudden death), however, the observed relative risk reduction was not statistically significant (21%  [95% CI −7% to 41%]). The second cycle of BPLTTC also addressed the question of whether more versus less BP reduction confers additional advantages, and for the outcome of CHD alone, the result was inconclusive. 20 However, the weighted mean BP differences among randomized groups within each trial appeared to correlate well with the magnitude of reduction of CHD risk (Fig. 14-4). Furthermore, there was no evidence of statistical heterogeneity between those with and without diabetes. 21

Before the most recent evidence provided by the ADVANCE trial and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, Mancia and Grassi summarized the effects of BP-lowering drugs in patients with diabetes, focusing on entry and on-treatment BP levels (Fig. 14-5). As can be seen, few data existed in relation to achieved SBP levels below 135 mm Hg, despite prevailing guideline recommendations.

The ACCORD trial was specifically designed to address a question of appropriate target BP levels in people with T2DM. This was a factorially randomized trial of 10,251 individuals with T2DM from 77 centers in North America. 34–36 Participants with a hemoglobin A1c (HbA1c) of 7.5% or more and aged 40 years or older with cardiovascular disease or 55 years or older with anatomic evidence of significant atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two additional risk factors for cardiovascular disease (dyslipidemia, hypertension, smoking, or obesity) were randomized to intensive glucose control (aiming for HbA1c levels ≤6.0%) or standard control (aiming for HbA1c levels of 7.0% to 7.9%) (see also Chapter 13). Subsets of participants were also included in a factorially randomized evaluation of a BP-lowering intervention (n = 4733) or a lipid management intervention (n = 5518). The objective of the BP-lowering component of the study was to specifically examine the effects of targeting different SBP levels (an SBP target of 120 mm Hg or less, compared with 140 mm Hg or less). Participants who had SBP between 130 and 180 mm Hg on three or fewer antihypertensive medications and with no evidence of greater than 1.0 g of proteinuria per day or the equivalent were included. The BP-lowering regimen was at the physician’s discretion but included any class of drug therapy known to produce cardiovascular benefits (ACE inhibitors, ARBs, diuretics, calcium channel blockers, or beta blockers). The primary outcome was a composite of major cardiovascular events defined as nonfatal MI, nonfatal stroke, and cardiovascular death. Secondary outcomes included all coronary events, all stroke events, and all-cause death, considered separately.

The mean baseline BP in ACCORD was 139/76 mm Hg, and at study entry, 87% of participants were already taking some form of antihypertensive therapy. Over a mean follow-up of 4.7 years, intensive therapy achieved an SBP

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**FIGURE 14-4 Associations of BP differences between groups with risks of CHD in seven published randomized trials comparing more versus less intensive blood pressure control.** The circles are plotted at the point estimate of effect for the relative risk for every event type and the mean follow-up BP among randomized groups. (From Turnbull F; Blood Pressure Lowering Treatment Trialists’ Collaboration: Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials, Lancet 362:1527–1535, 2003.)
FIGURE 14-5 Effects of BP-lowering treatment on systolic and diastolic BP in patients with diabetes and hypertension in a number of trials before the ADVANCE and ACCORD trials. Values at trial entry and during treatment are shown for each trial. Dashed horizontal lines refer to goal BP values indicated by contemporary guidelines to be achieved during treatment. (Reproduced with permission from Mancia G, Grassi G: Systolic and diastolic blood pressure control in antihypertensive drug trials, J Hypertens 20:1461-1464, 2002.)

of 119 mm Hg compared with 134 mm Hg in the standard therapy group, resulting in a mean between-group difference of 14.2 mm Hg. Despite this difference in SBP, intensive therapy did not result in a statistically significant reduction in major cardiovascular events (relative risk reduction [RRR] 12%; 95% CI –6 to 27%; P = 0.20) (Fig. 14-6). When the components of the composite outcome were considered separately, intensive therapy did not reduce major coronary events (which included unstable angina) or cardiovascular death, but significantly reduced major strokes by 41% (95% CI 11%–61%). There was no statistically significant effect of intensive BP therapy on all-cause mortality or heart failure. There was no evidence of heterogeneity in treatment effect in subgroups of participants defined by age, sex baseline history of cardiovascular disease, and use of BP-lowering therapy at study entry.

Many have interpreted the ACCORD trial as being “negative” with respect to the BP-lowering component, stimulating discussion that the current target of 130/80 mm Hg or lower promulgated by many guidelines may not be justified. However, notwithstanding the clear benefits of a more aggressive approach to BP lowering for stroke well below this threshold, the 95% CIs around the estimates of effect size for other cardiovascular events, including CHD, do not exclude substantial and clinically important beneficial effects (approximately one-quarter reduction, which would be broadly consistent with a 14-mm Hg difference in SBP based on epidemiologic data). It is important to note that with the event rates in the control arm of ACCORD being approximately one half those anticipated, the trial was ultimately substantially underpowered. Intensive BP lowering in ACCORD was associated with an increased number of serious adverse events attributed to BP-lowering drugs, compared with the standard therapy group; however, overall rates over an average period of almost 5 years of follow-up were low (3.3% versus 1.3%). Particular concerns have been raised about higher levels of serum creatinine and lower levels of estimated glomerular filtration rate postrandomization among intensive–BP treatment participants. This did not translate to differences in end-stage renal disease (2.5% versus 2.4%), and intensive BP-lowering therapy was associated with the development of numerically fewer cases of microalbuminuria and macroalbuminuria, the latter being significantly lower than the rates observed in the standard therapy group.

### Legacy Effects of Blood Pressure Lowering

In 2008, the UKPDS study reported data from post-trial annual follow-up for an additional 6 years undertaken for all study participants, without attempts to maintain therapies based on the original randomization. Long-term post-trial observational follow-up of the blood glucose–lowering arm demonstrated sustained, and in some cases newly emerged, reductions in clinical events associated with original randomization to intensive glucose control. (See also Chapter 13.) These benefits were observed despite convergence of HbA1c values within a year of post-trial monitoring. Similarly, the BP difference achieved between randomized arms during the trial was no longer apparent within 2 years of the longer-term follow-up. However, unlike the blood glucose intervention, the significant reductions in clinical events were lost during the additional observational period, without the emergence of any new benefits. A reasonable interpretation of these findings is that BP reduction needs to be maintained for the long-term benefits of such treatment to continue.

### New Drugs

In addition to relatively recent approvals of the direct renin inhibitor aliskiren and the angiotensin II type 1 receptor (AT1R) blocker azilsartan, a number of novel BP-lowering compounds are currently in clinical testing. These include dual-action AT1R inhibitors that also block either neutral endopeptidase or the endothelin A receptor; a dual inhibitor of neutral endopeptidase and endothelin-converting enzyme; an aldosterone synthase inhibitor; an antagonist of natriuretic peptide receptor A; and a soluble epoxide hydrolase inhibitor. As clinical data accumulate, the efficacy and comparative efficacy of the molecules that proceed to approval may be examined in the specific context of T2DM.
EFFICACY AND SAFETY OF RENAL SYMPATHETIC DENERVATION

A recently developed therapeutic approach for the treatment of hypertension is endovascular catheter technology that allows selective sympathetic denervation of the kidney by transluminal radiofrequency ablation. To date, the evaluation of efficacy and safety of this approach has been limited to populations with “resistant” primary hypertension, with persistently high levels of BP despite comprehensive combination drug therapy. The Symplicity HTN-2 trial is the first and only randomized study reported to date, including 106 patients (approximately 30% with T2DM) with baseline SBP levels of 160 mm Hg or greater (≥150 mm Hg in the presence of diabetes), despite the use of at least three BP-lowering agents. The between-group difference in the primary outcome of office-measured BP level at 6 months was large and highly statistically significant (33/11 mm Hg, \( P<0.0001 \)). No separate analyses were performed in the subgroup with T2DM. No serious safety concerns were identified in this small study, but larger studies are under way and new studies in patients with milder forms of hypertension are being planned. Such studies may include a focus on patients with T2DM; in the meantime, renal sympathetic denervation is best described as a highly promising intervention requiring more reliable data on long-term efficacy and safety. Its applicability to the vast majority of patients with diabetes and hypertension globally, who have limited access to basic drugs, is a broader debate that will also take place.

SUMMARY

Available evidence about the effect of BP management on CHD risk in patients with T2DM can be reasonably summarized in the following way.
Lifestyle interventions (targeting physical activity and dietary modification) in people with T2DM can favorably affect BP levels, and trials powered to assess effects on clinical outcomes are ongoing. However, effective implementation strategies to enact sustained positive lifestyle changes—including for dietary sodium restriction, which is likely to be particularly important—are generally lacking.

Placebo-controlled trials provide clear evidence that BP lowering among individuals with diabetes and hypertension results in a reduction in CHD incidence. The findings of the most recent and largest of these trials suggest that routine provision of BP-lowering therapy to patients with T2DM, regardless of initial BP level, is an effective strategy for reducing CHD risk.

Debate about comparative efficacy of BP-lowering drugs for the prevention of CHD in patients with diabetes continues. Although not unequivocal, there are some data to support additional benefits of ACE inhibitor–based regimens over others for the outcome of CHD.

Specifically for the outcome of CHD, trial evidence of the benefits of more intensive versus less intensive BP lowering is consistently suggestive, but not definitive to date. The ACCORD trial failed to show clear benefits on CHD of aggressive management to a SBP target of below 120 mm Hg, compared with an SBP target of 140 mm Hg or lower, but this comparison was underpowered to exclude sizeable, clinically important effects.

These conclusions, however, should be considered in the context of a number of important points. First, recommendations about BP-lowering treatment must take into account the known or likely effects on all relevant health outcomes and not just CHD. For example, the evidence that more intensive versus less intensive BP lowering provides greater protection against stroke in patients with or without diabetes is unequivocal, including large beneficial effects in preventing stroke observed in the ACCORD trial. Similarly, calcium channel blocker or thiazide-based regimens may be more important for the prevention of stroke, whereas ACE-inhibitor or ARB-based regimens are more protective against the microvascular renal complications of diabetes. The use of beta blockers might be regarded as essential in patients with prior myocardial infarction or systolic heart failure.

Thus, consideration of a number of individual patient characteristics that may be relevant to a broad range of clinical outcomes would be appropriate in making choices about the use of particular BP-lowering drug regimens in patients with T2DM.

Second, and related to this, is a general understanding of the paradigm for using of an assessment of an individual’s projected absolute risk of developing CHD (or stroke, or any cardiovascular disease) to help guide therapy. In the context of T2DM, this might be most relevant where uncertainty exists about the balance of potential risks and benefits in relation to the intensity of BP lowering in an individual patient. There are a number of clinical tools available to estimate CHD or CVD risk in people with T2DM, derived either from general populations or from specific populations with diabetes. 42-45 All have potential limitations including in relation to generalizability; nonetheless, they remain useful for clinical practice. 46,47

Finally, any ongoing uncertainty about the relative efficacy of therapeutic regimens or appropriate targets for BP reduction in people with T2DM closer to the “nontensive” range is dwarfed by the lack of knowledge about effective strategies to ensure that people with T2DM receive any BP-lowering therapy in the first place, let alone what might be considered ideal regimens or acceptable levels of BP control. The “practice gaps” are very large, particularly in the low- and middle-income countries that have the highest numbers of people with T2DM, but also in countries with rich economies. 48-54 From a global perspective, these issues will not be addressed by new clinical trials establishing the efficacy of new drugs or new combinations of drugs. Rather, the development, implementation, and rigorous evaluation of interventions at the level of policy, systems, and services will be crucial to ensure maximal gains in human health from what we already know about the treatment of BP in people with T2DM.

References