

Rationale and Design for the Blood Pressure Intervention of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial

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The Action to Control Cardiovascular Disease in Diabetes (ACCORD) blood pressure trial is an unmasked, open-label, randomized trial with a sample size of 4,733 participants. This report describes the rationale, design, and methods of the blood pressure interventions in ACCORD. Participants eligible for the blood pressure trial are randomized to 1 of 2 groups with different treatment goals: systolic blood pressure <120 mm Hg for the more intensive goal and systolic blood pressure <140 mm Hg for the less intensive goal. The primary outcome measure for the trial is the first occurrence of a major cardiovascular disease (CVD) event, specifically nonfatal myocardial infarction or stroke, or cardiovascular death during a follow-up period ranging from 4–8 years. The ACCORD blood pressure trial should provide the first definitive clinical trial data on the possible benefit of treating to a more aggressive systolic blood pressure goal in reducing CVD events in patients with diabetes mellitus. © 2007 Elsevier Inc. All rights reserved. (Am J Cardiol 2007;99[suppl]:44i–55i)

More than 4,700 of the participants enrolled in the Action to Control Cardiovascular Disease in Diabetes (ACCORD) trial were entered into the ACCORD blood pressure trial,

which randomly assigned participants to a more intensive systolic blood pressure goal of <120 mm Hg or a less intensive systolic blood pressure goal of <140 mm Hg, with the same primary cardiovascular disease (CVD) outcome as for the glycemic and lipid trials (major CVD mortality and morbidity).¹ The purposes of this report are (1) to describe the rationale and design for the blood pressure intervention component and (2) discuss the lessons learned in the vanguard phase of ACCORD that resulted in changes to the blood pressure protocol for the full-scale trial.

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Diabetes Mellitus, Blood Pressure, and Cardiovascular Disease

Diabetes mellitus increases the risk for CVD events 2- to 3-fold at every level of systolic blood pressure or diastolic blood pressure, and in patients with diabetes there is a graded increase in CVD risk across the entire range of blood pressure levels.^{2,3} Therefore, diabetes and hypertension combined confer a much greater risk than either condition alone. In part because of this greater risk, even at prehypertensive levels of blood pressure, the Seventh Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommended beginning drug treatment in patients with diabetes with systolic blood pressure ≥ 130 mm Hg or diastolic blood pressure ≥ 80 mm Hg, with a blood pressure treatment goal of <130/80 mm Hg.⁴ In fact, the same blood pressure goal has been recommended in nearly

every US or international guideline since 2000 that has recommended blood pressure goals for patients with diabetes. There is, however, a paucity of randomized clinical trial evidence (described later) to support these recommendations. Relying primarily on available evidence from clinical trials, the 2004 hypertension guidelines of the US Department of Veterans Affairs (VA) and the US Department of Defense (DoD) recommend a goal blood pressure in diabetes of <140/80 mm Hg.⁵

Trials of Reducing Blood Pressure in Patients with Diabetes

Randomized clinical trials of blood pressure lowering in patients with hypertension and diabetes that may be examined to address the question of blood pressure goals are listed in Table 1.^{6–14} In the 583 participants with type 2 diabetes in the Systolic Hypertension in the Elderly Program (SHEP), major CVD events were reduced by 34% in the actively treated group,⁶ which initiated treatment with the thiazide-type diuretic chlorthalidone in older participants with isolated systolic hypertension. Although this was the same relative risk reduction as in participants without diabetes, the absolute risk reduction was twice as great for participants with diabetes. The SHEP blood pressure entry criterion was systolic blood pressure 160–219 mm Hg; the treatment goal was <160 mm Hg and a ≥ 20 mm Hg reduction from baseline. In the subgroup of patients with diabetes, the achieved mean systolic blood pressure was 146 mm Hg in the actively treated group and 155 mm Hg in the placebo group, a systolic blood pressure difference of 9 mm Hg.

The Hypertension Optimal Treatment (HOT) study randomized participants with hypertension with elevated diastolic blood pressure to 1 of 3 groups, each with different blood pressure goals (≤ 90 , ≤ 85 , and ≤ 80 mm Hg). It was found that in the subgroup of patients with diabetes ($n = 1,501$), major CVD events were reduced by 51% ($p = 0.005$) in those randomized to the diastolic blood pressure goal of ≤ 80 mm Hg compared with the goal of ≤ 90 mm Hg: 12 versus 24 events/1,000 patient-years.^{8,9} However, this was a post hoc analysis, and the number of events (22 compared with 45 cardiovascular events, respectively) was relatively small. In this subgroup of patients with diabetes, the achieved mean blood pressure level in the group with the ≤ 80 mm Hg goal was 144/81 mm Hg, compared with 148/85 mm Hg in the group with the ≤ 90 mm Hg goal, a blood pressure difference of 4/4 mm Hg.⁸ There were no significant differences in CVD events between randomized groups in the entire group of 18,790 participants with hypertension in HOT.^{8,9}

In the United Kingdom Prospective Diabetes Study (UKPDS),^{10,11} 1,148 patients with hypertension and type 2 diabetes were randomized to either “tight blood pressure control” (<150/85 mm Hg) or “less tight blood pressure control” (<180/105 mm Hg). After a median follow-up period of 8.4 years,¹⁰ diabetes-related end points were re-

duced by 24% ($p = 0.005$), deaths related to diabetes by 32% ($p = 0.019$), strokes by 44% ($p = 0.013$), and microvascular end points by 37% ($p = 0.009$) in the group with the lower blood pressure goal compared with the less intensively treated group. Although the findings were not statistically significant, all-cause mortality was lower by 18% and myocardial infarction (MI) by 21% in the more intensively treated group. Average blood pressure over 9 years was 144/82 and 154/87 mm Hg in the tight and less-tight blood pressure control groups, respectively, a blood pressure difference of 10/5 mm Hg.

In another placebo-controlled trial of treatment of patients with isolated systolic hypertension, the Systolic Hypertension in Europe (Syst-Eur) trial, the 492 participants with diabetes were reported in a post hoc analysis to have significant reductions in CVD mortality, all CVD events, and stroke, with the mean systolic blood pressure reduced from 175 to 153 mm Hg, 9 mm Hg lower than in the placebo group, with active treatment based on the dihydropyridine calcium channel blocker (CCB) nitrendipine.⁷ Entry criteria were similar to those of SHEP (systolic blood pressure 160–219 mm Hg), and the goal was to reduce systolic blood pressure ≥ 20 mm Hg to <150 mm Hg.

The Appropriate Blood Pressure Control in Diabetes (ABCD) trial, a randomized trial in 470 participants with hypertension and type 2 diabetes, compared the effects of “moderate control of blood pressure” (target diastolic blood pressure 80–89 mm Hg) with those of “intensive control of blood pressure” (target diastolic blood pressure 75 mm Hg) on the incidence and progression of diabetic nephropathy, retinopathy, CVD, and neuropathy.^{12–14} The mean blood pressure achieved was 132/78 mm Hg in the intensive-control group and 138/86 mm Hg in the moderate-control group. There were no differences in any microvascular end points for the 2 blood pressure goal groups. The difference in blood pressure was 6/8 mm Hg, although the goals were only for diastolic blood pressure. The intensive-therapy group had a lower mortality rate, 5.5% versus 10.7% ($p = 0.037$), but there were no statistically significant differences in MI, cerebrovascular events, or heart failure to account for the mortality difference.¹⁴ Because of the small sample size, the multiple comparisons performed, and the absence of benefit for CVD or renal outcomes, the mortality difference seen in ABCD should be interpreted cautiously.

Therefore, HOT and UKPDS provide the strongest clinical trial evidence to date and support blood pressure level goals in patients with diabetes and hypertension of <150/85 mm Hg (UKPDS) and diastolic blood pressure <80 mm Hg (HOT). In the 2 studies, the achieved mean systolic blood pressure in the more intensively treated groups was 144 mm Hg. On the basis of these goals and achieved blood pressure levels, as well as achieved systolic blood pressure levels in other trials, including SHEP (146 mm Hg), all of the trials are consistent with systolic blood pressure goals approaching 140 mm Hg in patients with diabetes, and none, including ABCD, has confirmed benefit to goals lower than this.

Table 1
Clinical trials of blood pressure (BP) lowering in patients with diabetes mellitus

| Trial | N | Duration (yr) | Mean BP (mm Hg) | | Initial Therapy | Outcome | RRR |
|------------------------|-------|---------------|-----------------|----------------|--------------------------|---|-----------------------------------|
| | | | Less Intensive | More Intensive | | | |
| SHEP ⁶ | 583 | 5 | 155/72* | 146/68* | Chlorthalidone | Stroke CVD events CAD | 22% (NS) 34% 56% |
| Syst-Eur ⁷ | 492 | 2 | 162/82 | 153/78 | Nitrendipine | Stroke CV events | 69% 62% |
| HOT ^{8,9} | 1,501 | 3 | 148/85 | 144/81 | Felodipine | CV events MI Stroke CV mortality | 51% 50% 30% (NS) 67% |
| UKPDS ^{10,11} | 1,148 | 8.4 | 154/87 | 144/82 | Captopril or atenolol | Diabetes-related end points Deaths Stroke Microvascular | 24% 32% 44% 37% |
| ABCD ¹²⁻¹⁴ | 470 | 5.3 | 138/86 | 132/78 | Nisoldipine or enalapril | C _{Cr} Albuminuria Retinopathy Neuropathy Mortality MI, stroke, CHF | NC NC NC NC 49% NS |

ABCD = Appropriate Blood Pressure Control in Diabetes trial; CAD = coronary artery disease; C_{Cr} = creatine clearance; CHF = congestive heart failure; CV = cardiovascular; CVD = CV disease; HOT = Hypertension Optimal Treatment trial; MI = myocardial infarction; NC = no change; NS = not significant; RRR = relative risk reduction; SHEP = Systolic Hypertension in the Elderly Program; Syst-Eur = Systolic Hypertension in Europe trial; UKPDS = United Kingdom Prospective Diabetes Study.

* Courtesy of Sara Pressel, School of Public Health, University of Texas Health Science Center, Houston, Texas.

Table 2
Distribution of randomizations in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial

| Glycemia Trial | BP Trial | | Lipid Trial* | | Total |
|-----------------------------|----------------|----------------|--------------|---------|--------|
| | SBP <120 mm Hg | SBP <140 mm Hg | Group A | Group B | |
| HbA _{1c} <6.0% | 1,178 | 1,193 | 1,383 | 1,374 | 5,128 |
| HbA _{1c} 7.0%–7.9% | 1,184 | 1,178 | 1,370 | 1,391 | 5,123 |
| Total | 2,362 | 2,371 | 2,753 | 2,765 | |
| | | 4,733 | | 5,518 | 10,251 |

BP = blood pressure; HbA_{1c} = glycosylated hemoglobin; SBP = systolic BP.

* Treatment group assignments are blinded until the end of the trial.

The ACCORD blood pressure trial was designed to test the effect on CVD morbidity and mortality of blood pressure lowering in addition to glycemetic control in patients with diabetes. ACCORD should provide the first definitive clinical trial data on the possible benefit of treating to more aggressive blood pressure goals (compared with UKPDS, for example) in preventing CVD in patients with diabetes. Although the Action in Diabetes and Vascular Disease (ADVANCE) trial is testing the effect of blood pressure lowering on CVD events in participants with diabetes, whether or not they have hypertension, by adding fixed blood pressure-lowering therapy with the angiotensin-converting enzyme (ACE) inhibitor perindopril plus the thiazide-type diuretic indapamide to one randomized group and matching placebo to the other, it does not treat to a specific blood pressure goal.¹⁵

Action to Control Cardiovascular Risk in Diabetes Blood Pressure Trial: Objective and Overall Design

The overall goal of the ACCORD trial is to test 3 complementary medical treatment strategies for reducing the rate of major CVD morbidity and mortality in patients with type 2 diabetes.¹ It was designed as a randomized, multicenter, double 2 × 2 factorial trial in 10,000 patients with type 2 diabetes. Ultimately, 10,251 participants were recruited (Table 2). The trial is designed to test the effects on preventing major CVD events of intensive glycemetic control, treatment to increase high-density lipoprotein cholesterol and lower triglycerides (in the context of good low-density lipoprotein cholesterol and glycemetic control), and intensive blood pressure control (in the context of good glycemetic control). All 10,251 participants are in the

glycemia trial. In addition, one 2×2 trial will also address the lipid question in 5,518 of the recruited participants, and the other 2×2 trial will address the blood pressure question in 4,733 participants. Therefore, each participant will be in a 2×2 trial testing 2 treatment strategies of 2 interventions, one of which is always glycemic control and the other either lipid or blood pressure control.

The primary outcome measure for the trial is the first occurrence of a major CVD event, specifically nonfatal MI or stroke, or cardiovascular death. Participants were recruited over 2 noncontiguous periods (a vanguard phase and the main trial), and follow-up is planned for about 4–8 years (approximate mean, 5.6 years).

The blood pressure component of ACCORD is an unmasked, open-label, randomized trial with an original target sample size of 4,200 participants, although 4,733 were eventually recruited. Participants eligible for the blood pressure component were randomized to 1 of 2 groups with different treatment goals: systolic blood pressure <120 mm Hg for the more intensive goal and systolic blood pressure <140 mm Hg for the less intensive goal. For ACCORD participants not included in the blood pressure portion of ACCORD (ie, the 5,518 participants in the lipid portion of the trial), recommendations for blood pressure treatment are referred to their usual sources of care.

The specific primary ACCORD blood pressure research question is the following: In middle-aged or older men and women with type 2 diabetes who are at high risk for having a CVD event, in the context of good glycemic control, does a therapeutic strategy that targets a systolic blood pressure of <120 mm Hg reduce the rate of CVD events more than a strategy that targets a systolic blood pressure of <140 mm Hg?

Several secondary hypotheses will be tested for each of the interventions, including the blood pressure intervention. The hypotheses are to determine whether more intensive treatment compared with standard treatment reduces the occurrence of (1) an expanded macrovascular disease outcome, consisting of the primary outcome plus coronary revascularization plus hospitalization for heart failure; (2) total mortality; (3) each of the separate components of the primary outcome: CVD mortality, major coronary artery disease event (fatal or nonfatal), or stroke (fatal or nonfatal); (4) congestive heart failure death or hospitalization for congestive heart failure; and (5) a composite microvascular disease outcome, including kidney and eye disease.

Health-related quality of life and cost-effectiveness will also be examined as secondary outcomes.¹⁶ In addition, there are also eye and cognitive functioning substudies.^{17,18} Whether >1 of the more intensive treatment groups experiences a significantly lower major CVD event rate than the respective control groups or not, clinicians' choices may be further guided by (1) effects on secondary clinical outcomes, including microvascular disease, adverse effects, and the quality of life; (2) subgroup analyses of effects in combined versus single-factor approaches; (3) resource re-

quirements, including medical care costs; and (4) patients' acceptance and tolerance of various classes of medications.

Participant Selection

In addition to fulfilling the required glycemia trial entry criteria, to be eligible for ACCORD, a screenee also needed to fulfill the entry criteria for the lipid and/or blood pressure component of the trial.

The inclusion criteria for the overall glycemia trial are described in detail elsewhere in this supplement.¹ In brief, participants must have a diagnosis of type 2 diabetes for ≥ 3 months before randomization, defined according to the 1997 American Diabetes Association (ADA) criteria¹⁹ and must be at high risk for CVD events. The blood pressure inclusion criteria aimed to recruit participants, whether treated for hypertension or not, who were likely to be able to have their systolic blood pressure maintained in the range of 135–139 mm Hg if randomized to the standard systolic blood pressure group or who were likely to be able to achieve the systolic blood pressure goal of <120 mm Hg with antihypertensive drug therapy. Therefore, participants eligible for the glycemic component of the trial were also eligible for the blood pressure component if (1) their systolic blood pressures were between 130 and 160 mm Hg, inclusive, and they were taking 0, 1, 2, or 3 antihypertensive medications; (2) their systolic blood pressures were between 161 and 170 mm Hg, inclusive, and they were taking 0, 1, or 2 antihypertensive medications; or (3) their systolic blood pressures were between 171 and 180 mm Hg, inclusive, and they were taking 0 or 1 antihypertensive medication. Additional eligibility requirements included dipstick protein in a spot urine sample $<2+$, protein-creatinine ratio in a spot urine sample <700 mg protein/1 g creatinine, or 24-hour protein excretion <1.0 g/24 hr, because there is some evidence that patients with chronic kidney disease and urine protein excretion ≥ 1 g/24 hr have a slower rate of decrease in renal function with blood pressure of approximately 125/75 mm Hg.²⁰

If an investigator believed that a participant was likely to be eligible for the blood pressure intervention, medications may have been adjusted by the ACCORD clinic before the randomization visit to determine whether the participant's systolic blood pressure would increase or decrease to the blood pressure eligibility criteria. No more than 2 visits after any adjustment of any antihypertensive therapy were permitted for a participant to meet the blood pressure eligibility criteria before entry into ACCORD. For screenees who were not on blood pressure-lowering medications and were previously untreated for hypertension, there must have been documentation of systolic blood pressure ≥ 130 mm Hg on ≥ 2 occasions. There were no diastolic blood pressure inclusion criteria, because in older individuals systolic blood pressure is a stronger predictor of cardiovascular events than diastolic blood pressure, and if systolic blood pressure is controlled for, diastolic blood pressure is inversely related to risk.²¹ The general exclusion criteria

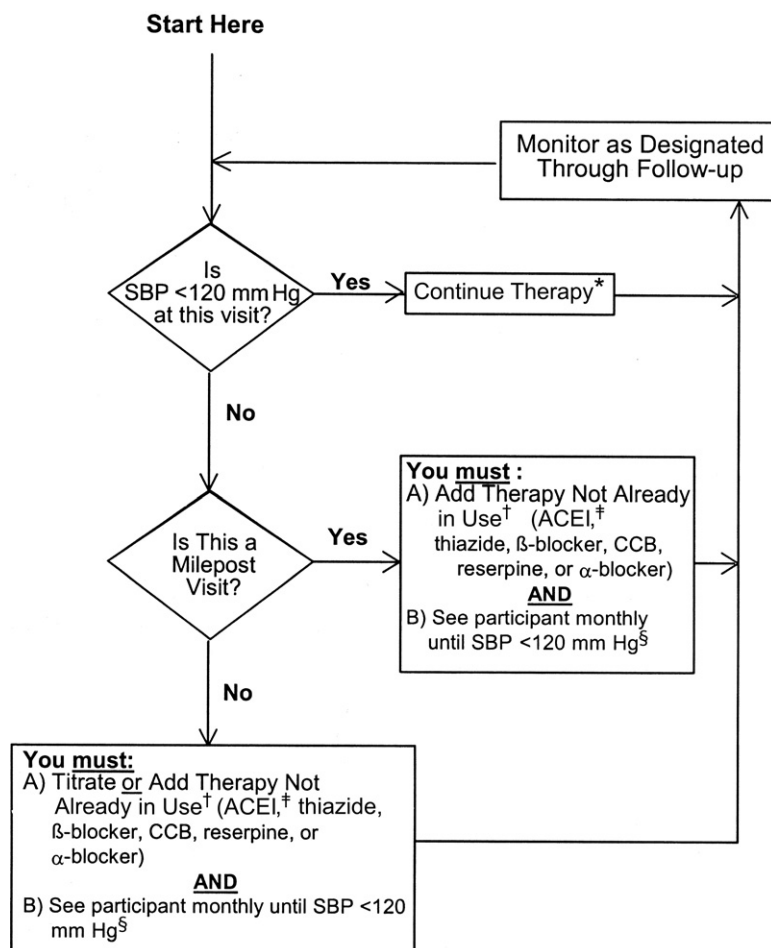


Figure 1. Treatment algorithm for the group with intensive blood pressure control (goal: systolic blood pressure [SBP] <120 mm Hg). ACEI = angiotensin-converting enzyme inhibitor; CCB = calcium channel blocker. *Unless side effects warrant a change in therapy. †Consult with the clinical center network before adding a fifth antihypertensive medication. ‡Angiotensin II receptor blockers can be considered as substitutes for participants who do not tolerate ACEIs. §Consult with the clinical center network until a clinical decision is made that therapy should not be increased further.

for ACCORD are described elsewhere.¹ There are no additional exclusions for the blood pressure trial.

Use of Antihypertensive Drugs

Figures 1 and 2 describe the treatment algorithms for the 2 blood pressure treatment groups. The use of once-daily preparations of the study antihypertensive agents is encouraged unless an alternative dosing frequency (eg, twice daily) is indicated. The following classes of agents are provided by the study: ACE inhibitors, diuretics, β -blockers, dihydropyridine and nondihydropyridine CCBs, α -blockers, angiotensin II receptor blockers (ARBs), sympatholytics, α -/ β -blockers, and the following combinations: a thiazide diuretic and a potassium-sparing diuretic, a β -blocker and a diuretic, an ACE inhibitor and a diuretic, an ARB and a diuretic, and a dihydropyridine CCB and an ACE inhibitor.

The aim is to achieve the blood pressure goal. To achieve this, a study therapist may select among the available

ACCORD antihypertensive medications for the initiation of therapy. Other drugs not supplied by the trial may also be used as an investigator deems appropriate. However, all antihypertensive regimens should include a drug class associated with reduced cardiovascular events in participants with diabetes: a diuretic, a β -blocker, a CCB, an ACE inhibitor, or an ARB.^{4,22–25} Because there is no such evidence for the α -blockers, when an α -blocker is used, it is used in combination with ≥ 1 agent proved to reduce cardiovascular events in patients with hypertension and diabetes.²³

Although several guidelines²⁶ recommend treating patients with diabetes and hypertension with ACE inhibitors or ARBs, it is acknowledged that there is no conclusive evidence for this preference, except for nephropathy with macroalbuminuria,²⁷ and JNC 7 concluded that “clinical trials with diuretics, ACE inhibitors, β -blockers, ARBs, and calcium antagonists have demonstrated benefit in the treatment of hypertension in both type 1 and type 2 [diabetes].”^{4,22} However, the ACCORD study recommends the use of ACE inhibitors to reduce cardiovascular morbidity

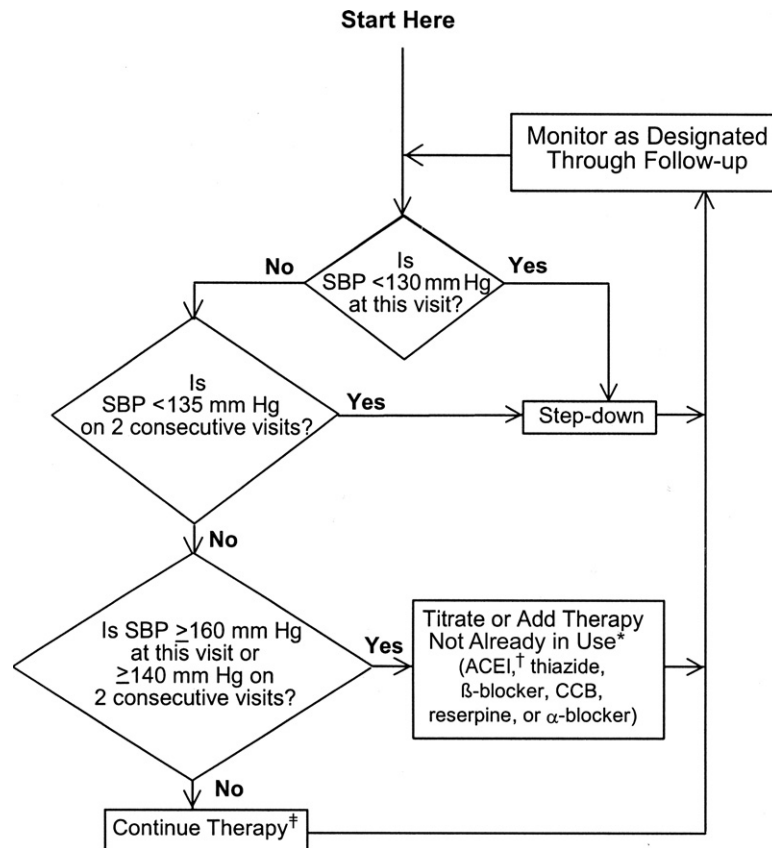


Figure 2. Treatment algorithm for the group with standard blood pressure control (goal: systolic blood pressure [SBP] <140 mm Hg). ACEI = angiotensin-converting enzyme inhibitor; CCB = calcium channel blocker. *Consult with the clinical center network before adding a fifth antihypertensive medication. †Angiotensin II receptor blockers can be considered as substitutes for participants who do not tolerate ACEIs. ‡Unless side effects warrant a change in therapy.

and mortality in patients who have experienced acute MI,²⁸ heart failure,²⁹ or nephropathy^{27,30,31} or in patients with type 2 diabetes with ≥ 1 additional risk factor for CVD, based in part on the results in the subgroup of patients with diabetes (including those without hypertension) of the Heart Outcomes Prevention Evaluation (HOPE) study.³²

Intensive Blood Pressure Control

The blood pressure treatment protocol of ACCORD is designed to be flexible in terms of the choice and doses of drugs. For participants in the intensive blood pressure control group (Figure 1), the recommendation is to start with a combination of a diuretic and either an ACE inhibitor or a β -blocker at randomization. Drug doses are increased and/or additional antihypertensive medications are added at each subsequent visit in the intensive group until a participant's goal has been reached.

The blood pressure and glycemic treatments begin at the time of randomization. Intensive-group participants are then seen at least monthly until achieving the blood pressure goal (systolic blood pressure <120 mm Hg). Regular visit schedules differ by treatment group assignment. For participants in

the intensive blood pressure control group or the standard blood pressure control group and the intensive glycemic control group, postrandomization visits occur at least at months 1, 2, 3, and 4, and every 2 months thereafter. For participants in the standard blood pressure control group and the standard glycemic control group, postrandomization visits occur at months 1 and 4, and every 4 months thereafter. Additional visits can be scheduled as needed to monitor and ensure the appropriate implementation of the study interventions.

For the intensive blood pressure control group, the algorithm is structured to focus on adding additional medications for those intensive-group participants who are above their blood pressure goal (systolic blood pressure <120 mm Hg) at the "milepost visits." At the point of randomization, all participants in the intensive group of the hypertension study will automatically be assigned a series of milepost visits dates, scheduled at 4-month intervals for the first 2 years of follow-up and annually thereafter. At a milepost visit, if systolic blood pressure is not <120 mm Hg, adding an antihypertensive drug from a different class than what is being taken is mandated. Adding a drug should be done unless there is a compelling reason not to do so. If a therapist believes that there is such a compelling reason, it must be documented on a "milepost exception form." Milepost dates are assigned for the entire

duration of the study. Between these designated visits, an ACCORD therapist may intensify therapy for participants not at goal either by adjusting the doses of medications within the recommended dose ranges or by adding medications. However, once a milestone date has been reached and a participant remains above goal blood pressure, a therapist is required to add an additional class of drug to the existing regimen. Milepost visits apply only to the intensive blood pressure control group.

Each clinic and individual participant has his or her blood pressure and drug status monitored closely by the Coordinating Center and the clinical center network (CCN). The number of milestone exception forms is closely monitored at each ACCORD clinic, and regular feedback is provided to the clinic for the degree of adherence to the drug protocol.

For intensive-group participants who have been prescribed 5 drugs, if blood pressure remains above the goal at subsequent milestone visits, therapists are permitted to substitute different classes into the regimen instead of adding other drugs. It is expected that most ACCORD participants in the intensive blood pressure control group will require ≥ 2 and up to 5 antihypertensive medications to achieve their blood pressure goals. If a participant is not at goal with 4 drugs, consultation with one of the CCN's hypertensive specialists is recommended.

In summary, action is required at each milestone visit throughout the duration of the study for those intensive-group participants who remain above their initial goal pressure of <120 mm Hg. Also, if systolic blood pressure is ≥ 120 mm Hg at any regular clinic visit for a participant in the intensive blood pressure control group, blood pressure medications must be added or titrated and the participant seen monthly until systolic blood pressure decreases to <120 mm Hg or until a clinical decision is made that therapy should not be increased further (see Figure 1).

Standard Blood Pressure Control

For standard blood pressure control group participants (Figure 2), medication dose titration or the addition of another drug is indicated if systolic blood pressure is ≥ 160 mm Hg at a single visit or ≥ 140 mm Hg at 2 successive visits.

The standard blood pressure treatment protocol in ACCORD is designed to reduce systolic blood pressure to a goal of <140 mm Hg, on the basis of evidence from UKPDS^{10,11} and HOT.^{8,9} Mean systolic blood pressure in the intensive blood pressure groups in these 2 trials averaged 144 mm Hg. Because it is not known if lowering systolic blood pressure to the more intensive ACCORD goal of <120 mm Hg, compared with the standard goal of <140 mm Hg, is beneficial or even harmful in patients such as those entered into the ACCORD trial, careful step-down (a reduction of the dose or number of antihypertensive drugs) is allowed by protocol for participants in the standard group. Downtitration or step-down is carried out at the discretion of ACCORD therapists,

after consultation with participants. The criterion permitting downtitration is systolic blood pressure <135 mm Hg at 2 successive clinic visits or systolic blood pressure <130 mm Hg at any single visit (Figure 2).

The purposes of the titration and downtitration are (1) to produce a mean systolic blood pressure in the standard blood pressure control group of 130–139 mm Hg, which we believe is ethical on the basis of current evidence from the randomized trials of blood pressure reduction in patients with diabetes, and (2) to produce a ≥ 10 mm Hg difference in mean systolic blood pressure levels between the participants in the intensive blood pressure control and standard blood pressure control group.

Management of Adverse Effects and Combination Regimens

Medication doses may be decreased or medications changed whenever an ACCORD therapist considers it clinically indicated, such as when symptoms are reported that could be secondary to an antihypertensive medication. Rechallenge is encouraged if a period off a medication is not associated with the resolution of the symptoms or if the adverse experience is not serious and the agent is strongly indicated for another condition (eg, an ACE inhibitor for heart failure).

Combination regimens are encouraged that include a diuretic as one of the agents and that include drugs that have different mechanisms of action.³³ Only rarely are specific combinations discouraged, such as a β -blocker with the nondihydropyridine CCBs verapamil or diltiazem (for safety reasons).

Lessons Learned in the Vanguard Phase and Changes in Protocol

Recruitment occurred in 2 noncontiguous periods: an initial period that began in January 2001 in the vanguard phase of the trial, during which 1,174 participants were recruited to the overall glycemia trial, and then a subsequent full-scale recruitment period from February 2003 (after review of the vanguard data) to October 29, 2005 (during which the remainder of the 10,251 participants were recruited).

During the vanguard phase, the ACCORD investigators, the Data and Safety Monitoring Board (DSMB), and the National Heart, Lung, and Blood Institute (NHLBI) monitored the feasibility of the vanguard protocol. After extensive review of the data, the ACCORD protocol was revised to increase the likelihood of achieving all of the trial's objectives and was approved to proceed into the full-scale trial.

The purpose of the vanguard phase was to determine the feasibility and success of implementing the protocol treatments and of achieving the treatment goals and group blood pressure differences throughout the ACCORD clinical sites. The following were the specific goals of the vanguard phase blood pressure intervention, which were used to judge its success:

1. The study target systolic blood pressure goals for the randomized blood pressure arms were 20 mm Hg apart, <120 and <140 mm Hg. Epidemiologic evidence suggested that a 10–12 mm Hg difference should result in a 20% effect on CVD events. In addition, in previous blood pressure goal studies, the blood pressure differences achieved were approximately 50% of the targeted blood pressure goal differences.⁷ Therefore, the main criterion for success for the end of the vanguard period was a difference in mean systolic blood pressure between the intensive control and standard-control groups of ≥ 10 mm Hg.
2. An achieved mean systolic blood pressure level of <130 mm Hg in the intensive blood pressure control group was considered adequate for the vanguard phase, if it also was 10 mm Hg lower than that achieved in the standard blood pressure control group.

Utility of the Vanguard Phase

The vanguard phase of the blood pressure intervention permitted an evaluation of the appropriateness, effectiveness, feasibility, and safety of the eligibility criteria and the blood pressure intervention algorithms. The 491 participants in the vanguard blood pressure trial were incorporated into the main trial with only slight changes in the protocol.

Both of the specific vanguard blood pressure trial goals were met, and the DSMB recommended that the blood pressure study proceed to the full-scale phase. Participant adherence and tolerance in the blood pressure intervention were excellent because any medications with serious or bothersome adverse effects could be reduced in dosage or discontinued and replaced with other antihypertensive medications. Therefore, to increase the range of patients with diabetes to which the results of the glycemic and blood pressure interventions could be generalized, and to facilitate recruitment into the blood pressure trial, the eligibility criteria for blood pressure and the number of drugs were expanded from a maximum of 2 antihypertensive drugs (0–2 drugs) for systolic blood pressure of 130–160 mm Hg and a maximum of 1 drug (0–1 drug) for systolic blood pressure of 161–170 mm Hg to a maximum of 3 drugs (0–3 drugs) for systolic blood pressure of 130–160 mm Hg, 2 drugs (0–2 drugs) for systolic blood pressure of 161–170 mm Hg, and 1 drug (0–1 drug) for systolic blood pressure of 171–180 mm Hg.

Conclusion

The ACCORD blood pressure trial is designed to answer the question of whether, in participants with diabetes and elevated systolic blood pressure and in the context of good glycemic control, a therapeutic strategy that targets systolic

blood pressure <120 mm Hg will reduce the rate of CVD events more than a strategy that targets systolic blood pressure <140 mm Hg. The final recruited sample size ($n = 4,733$) to test how low a target blood pressure should be established to treat patients with diabetes is larger than the total of all the previous studies shown in Table 1 ($n = 4,194$). The ACCORD results should not only have implications for those with diabetes but, if positive, also lend strong support for further trials to address lower systolic blood pressure goals in other populations.

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Appendix

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