ORIGINAL ARTICLE

Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus

The ACCORD Study Group*

ABSTRACT

BACKGROUND

There is no evidence from randomized trials to support a strategy of lowering systolic blood pressure below 135 to 140 mm Hg in persons with type 2 diabetes mellitus. We investigated whether therapy targeting normal systolic pressure (i.e., <120 mm Hg) reduces major cardiovascular events in participants with type 2 diabetes at high risk for cardiovascular events.

METHODS

A total of 4733 participants with type 2 diabetes were randomly assigned to intensive therapy, targeting a systolic pressure of less than 120 mm Hg, or standard therapy, targeting a systolic pressure of less than 140 mm Hg. The primary composite outcome was nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. The mean follow-up was 4.7 years.

RESULTS

After 1 year, the mean systolic blood pressure was 119.3 mm Hg in the intensive-therapy group and 133.5 mm Hg in the standard-therapy group. The annual rate of the primary outcome was 1.87% in the intensive-therapy group and 2.09% in the standard-therapy group (hazard ratio with intensive therapy, 0.88; 95% confidence interval [CI], 0.73 to 1.06; P=0.20). The annual rates of death from any cause were 1.28% and 1.19% in the two groups, respectively (hazard ratio, 1.07; 95% CI, 0.85 to 1.35; P=0.55). The annual rates of stroke, a prespecified secondary outcome, were 0.32% and 0.53% in the two groups, respectively (hazard ratio, 0.59; 95% CI, 0.39 to 0.89; P=0.01). Serious adverse events attributed to antihypertensive treatment occurred in 77 of the 2362 participants in the intensive-therapy group (3.3%) and 30 of the 2371 participants in the standard-therapy group (1.3%) (P<0.001).

CONCLUSIONS

In patients with type 2 diabetes at high risk for cardiovascular events, targeting a systolic blood pressure of less than 120 mm Hg, as compared with less than 140 mm Hg, did not reduce the rate of a composite outcome of fatal and nonfatal major cardiovascular events. (ClinicalTrials.gov number, NCT00000620.)

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Diabetes mellitus increases the risk of cardiovascular disease by a factor of two to three at every level of systolic blood pressure.[1] Because cardiovascular risk in patients with diabetes is graded and continuous across the entire range of levels of systolic blood pressure, even at prehypertensive levels, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommended beginning drug treatment in patients with diabetes who have systolic blood pressures of 130 mm Hg or higher, with a treatment goal of reducing systolic blood pressure to below 130 mm Hg.[1-3] There is, however, a paucity of evidence from randomized clinical trials to support these recommendations. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) blood pressure trial (ACCORD BP)[4] tested the effect of a target systolic blood pressure below 120 mm Hg on major cardiovascular events among high-risk persons with type 2 diabetes. We present here the main results of the ACCORD BP trial.

Methods

Study Design

ACCORD was a randomized trial conducted at 77 clinical sites organized into seven networks in the United States and Canada (for a full list of participating institutions and investigators, see Section 1 in Supplementary Appendix 1, available with the full text of this article at NEJM.org). The trial enrolled 10,251 high-risk participants with type 2 diabetes mellitus.[5] All participants were randomly assigned to either intensive or standard glycemic control (the ACCORD glycemia trial). In addition, 5518 of the ACCORD participants were also randomly assigned (in a 2-by-2 factorial design) to either simvastatin plus fenofibrate or simvastatin plus placebo (the ACCORD lipid trial), and the remaining 4733 participants were also randomly assigned (in a 2-by-2 factorial design) to either intensive or standard blood-pressure control (the ACCORD blood-pressure trial). Details of the randomization are provided in Section 3 of Supplementary Appendix 1. The trial was sponsored by the National Heart, Lung, and Blood Institute (NHLBI). The protocol was approved by the institutional review board or ethics committee at each center and by an independent protocol review committee appointed by the NHLBI. The main results of the ACCORD glycemia trial have been published previously,[6] and the main results of the ACCORD Lipid trial are published elsewhere in this issue of the *Journal*.[7] The ACCORD trial protocol and amendments are available in Supplementary Appendix 2.

Eligibility Criteria and Recruitment

Inclusion criteria for the glycemia trial are described in detail elsewhere.[5] In brief, participants were eligible if they had type 2 diabetes mellitus and a glycated hemoglobin level of 7.5% or more and were 40 years of age or older with cardiovascular disease or 55 years of age or older with anatomical evidence of a substantial amount of atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two additional risk factors for cardiovascular disease (dyslipidemia, hypertension, smoking, or obesity). Exclusion criteria included a body-mass index (the weight in kilograms divided by the square of the height in meters) of more than 45, a serum creatinine level of more than 1.5 mg per deciliter (132.6 μmol per liter), and other serious illness. Participants with a systolic blood pressure between 130 and 180 mm Hg who were taking three or fewer antihypertensive medications and who had the equivalent of a 24-hour protein excretion rate of less than 1.0 g were also eligible for the blood-pressure trial (see Section 4 in Supplementary Appendix 1).[8] All participants provided written informed consent.

Recruitment occurred during two noncontiguous periods: 491 participants in the blood-pressure trial were recruited from January 2001 through early June 2001 during a "vanguard" phase, and the remaining 4242 participants were recruited from January 2003 through October 2005 during the main trial phase. An upper age limit of 79 years was added to the eligibility criteria for the main trial recruitment.

Trial Procedures

The ACCORD BP trial was a nonblinded trial in which participants were randomly assigned to intensive therapy that targeted systolic blood pressures of less than 120 mm Hg or standard therapy that targeted systolic blood pressures of less than 140 mm Hg. Treatment strategies that are currently available in clinical practice were used to lower blood pressure. Randomization was performed centrally on the study's Web site with the use of permuted blocks to maintain concealment of future study-group assignments.

The approach to the management of blood

pressure has been described elsewhere.[4] The schedules of visits for the assessment and management of blood pressure differed according to treatment group. For participants in the intensive-therapy group, visits to assess blood pressure were scheduled once a month for 4 months and every 2 months thereafter; for participants in the standard-therapy group, visits were scheduled at months 1 and 4 and every 4 months thereafter. Additional visits were scheduled as needed in both groups to monitor and ensure appropriate implementation of the study intervention strategies. In both blood-pressure groups, participants who were assigned to intensive glycemic therapy had more frequent contacts for the management of glycemia, but blood pressure was not monitored at these additional visits.

The ACCORD BP trial was a study of a treatment strategy to achieve specific systolic blood-pressure goals, rather than an evaluation of any specific drug regimen. However, all the antihypertensive regimens were to include drug classes that had been shown to result in a reduction in cardiovascular events among participants with diabetes. Details of the assessment of blood pressure, the adjustment of medication doses, and antihypertensive drug regimens are provided in Sections 8 and 9 in Supplementary Appendix 1. Antihypertensive drugs were donated by Abbott Laboratories, AstraZeneca Pharmaceuticals, GlaxoSmithKline Pharmaceuticals, King Pharmaceuticals, Sanofi-Aventis U.S., and Novartis Pharmaceuticals. Sphygmomanometers were donated by Omron Healthcare. The companies that donated the drugs and devices had no role in the design of the study, the accrual or analysis of the data, or the preparation of the manuscript.

At the 4-month visits that both treatment groups were scheduled to attend, information on study outcomes and adverse events was ascertained, blood samples were obtained, and clinical examinations were performed. The occurrence of self-reported symptoms of swelling or of dizziness on standing during the previous month was assessed as part of a standardized symptom checklist that was administered at baseline and at 1, 3, and 4 years after randomization to a random sample of 969 participants who were assessed for health-related quality of life.

TRIAL OUTCOMES

The primary outcome for all three ACCORD trials was the first occurrence of a major cardiovascular event, which was defined as the composite of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. Prespecified secondary outcomes included the combination of the primary outcome plus revascularization or hospitalization for congestive heart failure (termed the "expanded macrovascular outcome"); the combination of a fatal coronary event, nonfatal myocardial infarction, or unstable angina (termed "major coronary disease events"); nonfatal myocardial infarction; fatal or nonfatal stroke; nonfatal stroke; death from any cause; death from cardiovascular causes; and hospitalization or death due to heart failure. Definitions of each prespecified end point and information regarding methods of ascertainment are included in Section 6 in Supplementary Appendix 1.

Since all the antihypertensive medications used in the trial were approved by the Food and Drug Administration and were used according to approved labeling, we limited detailed data collection on serious adverse events to those attributed by investigators to antihypertensive medications (see Section 7 in Supplementary Appendix 1). Clinical and laboratory variables, including serum potassium and creatinine levels and estimated glomerular filtration rate,[9] were also examined as potential adverse effects.

STATISTICAL ANALYSIS

With a planned sample size of 4200 participants, the ACCORD BP trial was designed to have 94% power to detect a 20% reduction in the rate of the primary outcome for participants in the intensive-therapy group, as compared with those in the standard-therapy group, assuming a two-sided alpha level of 0.05, a primary-outcome rate of 4% per year in the standard-therapy group, and a planned average follow-up of 5.6 years for participants who did not have an event. Since ACCORD was a factorially designed trial, the targeted number of participants and the determination of sample size were made under the assumption that the intensive glucose-lowering intervention would produce a 15% benefit.[5]

Statistical analyses were conducted at the coordinating center with the use of S-Plus software, version 8.0 (Insightful) or SAS software, version 9.1 (SAS Institute). Baseline characteristics and key safety outcomes were compared between the two study groups with the use of the chi-square test, Fisher's exact test, Wilcoxon rank-sum test, and the two-sample t-test.

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Overall (N=4733)	Intensive Therapy (N=2362)	Standard Therapy (N=2371)	P Value
Age — yr	62.2±6.9	62.2±6.8	62.2±6.9	0.82
Female sex — no. (%)	2258 (47.7)	1128 (47.8)	1130 (47.7)	0.95
Race or ethnic group — no. (%)†				
Non-Hispanic white	2864 (60.5)	1455 (61.6)	1409 (59.4)	0.13
Black	1142 (24.1)	561 (23.8)	581 (24.5)	0.56
Hispanic	330 (7.0)	159 (6.7)	171 (7.2)	0.53
Education — no./total no. (%)				0.18
Less than high school	771/4729 (16.3)	404/2359 (17.1)	367/2370 (15.5)	
High-school graduate or GED	1271/4729 (26.9)	606/2359 (25.7)	665/2370 (28.1)	
Some college	1530/4729 (32.4)	776/2359 (32.9)	754/2370 (31.8)	
College degree or higher	1157/4729 (24.5)	573/2359 (24.3)	584/2370 (24.6)	
Previous cardiovascular event — no. (%)	1593 (33.7)	804 (34.0)	789 (33.3)	0.58
Previous heart failure — no./total no. (%)	203/4683 (4.3)	109/2338 (4.7)	94/2345 (4.0)	0.28
Cigarette-smoking status — no./total no.(%)				0.94
Current	626/4728 (13.2)	314/2358 (13.3)	312/2370 (13.2)	
Former	1981/4728 (41.9)	992/2358 (42.1)	989/2370 (41.7)	
Never	2121/4728 (44.9)	1052/2358 (44.6)	1069/2370 (45.1)	
Weight — kg	92.0±18.6	92.1±19.4	91.8±17.7	0.57
Body-mass index	32.1±5.6	32.2±5.7	32.1±5.4	0.58
Blood pressure — mm Hg‡				
All participants				
Systolic	139.2±15.8	139.0±16.1	139.4±15.5	0.47
Diastolic	76.0±10.4	75.9±10.6	76.0±10.2	0.87
Participants taking no medication at screening				
Systolic	139.4±14.3	139.8±15.0	139.1±13.7	0.53
Diastolic	77.5±9.4	77.5±9.5	77.4±9.4	0.86
Participants taking at least one medication at screening				
Systolic	139.2±16.0	138.9±16.3	139.4±15.8	0.34
Diastolic	75.7±10.5	75.7±10.7	75.8±10.3	0.87
Duration of diabetes — yr				0.86
Median	10	9	10	
Interquartile range	5–15	5–15	5–15	
Glycated hemoglobin — %	8.3±1.1	8.4±1.1	8.3±1.1	0.08
Fasting plasma glucose — mg/dl	174.7±57.7	176.1±57.7	173.2±57.7	0.09
Cholesterol — mg/dl				
Total	192.8±44.7	194.1±45.1	191.4±44.3	0.04
Low-density lipoprotein	110.0±36.7	111.1±37.4	108.8±36.0	0.03
High-density lipoprotein				
Women	51.3±13.8	51.3±13.4	51.3±14.3	0.99
Men	41.7±11.8	41.4±11.2	42.0±12.4	0.17

Table 1. (Continued.)

Characteristic	Overall (N=4733)	Intensive Therapy (N=2362)	Standard Therapy (N=2371)	P Value
Plasma triglycerides — mg/dl				0.71
Median	147	147	147	
Interquartile range	98–226	98–227	98–224	
Potassium — mg/dl	4.5±0.7	4.5±0.5	4.5±0.8	0.73
Serum creatinine — mg/dl	0.9±0.2	0.9±0.2	0.9±0.2	0.98
Estimated GFR — ml/min/1.73 m^2	91.6±28.8	91.6±30.3	91.7±27.1	0.93
Ratio of urinary albumin (mg) to creatinine (g)				0.64
Median	14.3	14.6	14.0	
Interquartile range	6.9–44.8	7.0–43.7	6.9–45.8	

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. To convert the values for glucose to millimoles per liter, multiply by 0.055551. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for potassium to millimoles per liter, multiply by 0.2558. To convert the values for creatinine to micromoles per liter, multiply by 88.4. GED denotes general equivalency diploma, and GFR glomerular filtration rate.
† Race or ethnic group was self-reported, and participants could check multiple categories.
‡ Data were available for 4733 participants in the total cohort, 599 who were taking no medication at screening and 4134 who were taking one or more medications at screening.

Analyses of primary and secondary outcomes were performed with the use of time-to-event methods according to the intention-to-treat principle. Event rates are expressed as the percentage of events per follow-up year, taking into account the censoring of follow-up data. Kaplan–Meier estimates were used to calculate the proportion of participants who had an event during follow-up.

Occurrences of primary and secondary outcomes in the two study groups were compared with the use of hazard ratios and 95% confidence intervals. Two-sided P values were calculated with the use of likelihood-ratio tests from Cox proportional-hazards regression analyses. The Cox models contained a term representing study-group assignments plus terms accounting for the following prespecified stratifying variables: assignment to the intensive glucose-lowering intervention, each of the seven clinical-center networks, and the presence or absence of a previous cardiovascular event. Using the log of follow-up time as a time-dependent covariate, we found no evidence of important departures from the assumption of proportionality.[10] We examined the consistency of the intervention effect on the primary outcome among nine prespecified subgroups using statistical tests of interaction between the treatment effect and the subgroup within the Cox models.

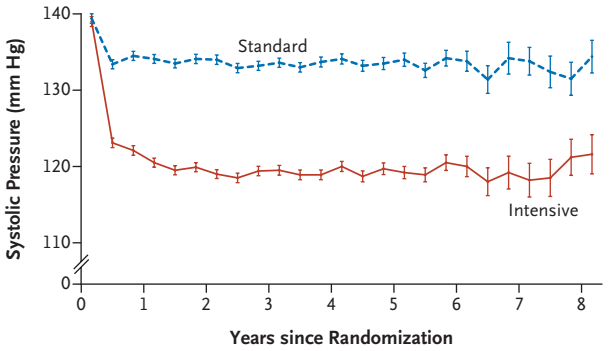
During the trial, an independent data and safety monitoring committee appointed by the NHLBI monitored the primary outcome (11 times) and total rate of death (7 times) with the use of O'Brien–Fleming boundaries determined by the Lan–DeMets approach. For these two outcomes, P values were adjusted to account for the number, timing, and results of interim analyses. All other P values for secondary outcomes and for subgroup analyses are nominal and have not been adjusted for multiple comparisons.

All analyses are based on observed data with the assumption that missing data were missing completely at random. For the longitudinal analysis of systolic blood pressure, a sensitivity analysis with the use of maximum-likelihood methods, under the assumption that the missing data were missing at random, is presented in Section 13 in Supplementary Appendix 1.

RESULTS

STUDY PARTICIPANTS

A total of 4733 participants were enrolled in the ACCORD BP trial. Of these, 2362 were randomly assigned to intensive blood-pressure control and 2371 were assigned to standard therapy. Baseline characteristics were generally similar between the two groups (Table 1). The mean age of the participants was 62.2 years; 47.7% were women and 33.7% had cardiovascular disease at base-



Mean No. of Medications Prescribed								
Intensive	3.2	3.4	3.4	3.5	3.5	3.5	3.4	3.4
Standard	1.9	2.1	2.1	2.2	2.2	2.3	2.3	2.3
No. of Patients								
Intensive	2174	2071	1973	1792	1150	445	156	156
Standard	2208	2136	2077	1860	1241	504	203	201

Figure 1. Mean Systolic Blood-Pressure Levels at Each Study Visit.
I bars indicate 95% confidence intervals.

line. The mean systolic and diastolic blood pressures of the participants at baseline were 139.2 mm Hg and 76.0 mm Hg, respectively.

At the end of the trial (June 2009), vital status was known for 95.1% of the randomly assigned participants. The mean duration of follow-up for the rate of death was 5.0 years, or 98.4% of the potential person-years of follow-up that would have been available if all surviving participants had been followed until the end of the trial. The mean duration of follow-up for the primary outcome was 4.7 years (94.8% of the potential follow-up). At the final follow-up visit, the rate of current smoking was 8.5% in the intensive-therapy group and 7.5% in the standard-therapy group (P=0.44).

BLOOD PRESSURE

The two therapeutic strategies quickly resulted in different systolic blood-pressure levels (Fig. 1). After the first year of therapy, the average systolic blood pressure at the 4-month protocol visits that both groups attended was 119.3 mm Hg (95% confidence interval [CI], 118.9 to 119.7) in the intensive-therapy group and 133.5 mm Hg (95% CI, 133.1 to 133.8) in the standard-therapy group, resulting in an average between-group difference of 14.2 mm Hg (95% CI, 13.7 to 14.7). The corresponding mean diastolic blood pressures were 64.4 (95% CI, 64.1 to 64.7) and 70.5 (95% CI, 70.2 to 70.8), for an average difference of 6.1 mm Hg (95% CI, 5.7 to 6.5) (Section 14 in Supplementary Appendix 1).

The lower blood pressure in the intensive-therapy group was associated with a greater exposure to drugs from every class (Fig. 1, and Section 11 in Supplementary Appendix 1). The mean number of medications after the first year was 3.4 (95% CI, 3.4 to 3.5) in the intensive-therapy group and 2.1 (95% CI, 2.1 to 2.2) in the standard-therapy group.

ADVERSE EVENTS

As compared with the standard-therapy group, the intensive-therapy group had significantly higher rates of serious adverse events attributed to antihypertensive treatment, as well as higher rates of hypokalemia and elevations in serum creatinine level (Table 2). The mean estimated glomerular filtration rates were significantly lower in the intensive-therapy group than in the standard-therapy group at the last visit. There were significantly more instances of an estimated glomerular filtration rate less than 30 ml per minute per 1.73 m^2 of body-surface area in the intensive-therapy group than in the standard-therapy group (99 vs. 52 events, P<0.001), although only 38 participants in the intensive-therapy group and 32 in the standard-therapy group had two or more instances of that rate (P=0.46). The frequency of macroalbuminuria at the final visit was significantly lower in the intensive-therapy group than in the standard-therapy group, and there was no between-group difference in the frequency of end-stage renal disease or the need for dialysis. In the random sample of 969 participants who were assessed for health-related quality of life, the frequency of symptoms of orthostatic hypotension was similar between the groups.

CLINICAL OUTCOMES

The primary composite outcome of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes occurred in 445 participants. The rate was 1.87% per year in the intensive-therapy group as compared with 2.09% per year in the standard-therapy group, with no significant between-group difference (hazard ratio with intensive therapy, 0.88; 95% CI, 0.73 to 1.06; P=0.20) (Table 3 and Fig. 2).

There were 294 deaths from any cause and 118 deaths from cardiovascular causes (Table 3). Rates of death from any cause were 1.28% per year in the intensive-therapy group and 1.19% in

Table 2. Serious Adverse Events and Clinical Measures after Randomization.*

Variable	Intensive Therapy (N=2362)	Standard Therapy (N=2371)	P Value
Serious adverse events — no. (%)†			
Event attributed to blood-pressure medications	77 (3.3)	30 (1.27)	<0.001
Hypotension	17 (0.7)	1 (0.04)	<0.001
Syncope	12 (0.5)	5 (0.21)	0.10
Bradycardia or arrhythmia	12 (0.5)	3 (0.13)	0.02
Hyperkalemia	9 (0.4)	1 (0.04)	0.01
Angioedema	6 (0.3)	4 (0.17)	0.55
Renal failure	5 (0.2)	1 (0.04)	0.12
End-stage renal disease or need for dialysis	59 (2.5)	58 (2.4)	0.93
Symptoms affecting quality of life — no./total no. (%)‡			
Hives or swelling	44/501 (8.8)	41/468 (8.8)	1.00
Dizziness when standing	217/501 (44.3)	188/467 (40.3)	0.36
Adverse laboratory measures — no. (%)			
Potassium <3.2 mmol/liter	49 (2.1)	27 (1.1)	0.01
Potassium >5.9 mmol/liter	73 (3.1)	72 (3.0)	0.93
Elevation in serum creatinine			
>1.5 mg/dl in men	304 (12.9)	199 (8.4)	<0.001
>1.3 mg/dl in women	257 (10.9)	168 (7.1)	<0.001
Estimated GFR <30 ml/min/1.73 m²	99 (4.2)	52 (2.2)	<0.001
Clinical measures§			
Glycated hemoglobin — %	7.6±1.3	7.5±1.2	0.13
Fasting plasma glucose — mg/dl	147.1±56.6	148.1±57.5	0.58
Plasma LDL cholesterol — mg/dl	98.7±40.3	96.8±37.8	0.10
Plasma HDL cholesterol — mg/dl	46.7±14.0	47.8±14.9	0.02
Plasma triglycerides — mg/dl			0.001
Median	138	131	
Interquartile range	97–210	92–197	
Potassium — mg/dl	4.3±0.5	4.4±0.5	0.17
Serum creatinine — mg/dl	1.1±0.4	1.0±0.5	<0.001
Estimated GFR — ml/min/1.73 m²	74.8±25.0	80.6±24.8	<0.001
Ratio of urinary albumin (mg) to creatinine (g)			<0.001
Median	12.6	14.9	
Interquartile range	6.4–41.7	7.0–56.8	
Microalbuminuria — no./total no. (%)	656/2174 (30.2)	712/2205 (32.3)	0.13
Macroalbuminuria — no. /total no. (%)	143/2174 (6.6)	192/2205 (8.7)	0.009
Weight — kg	93.3±21.2	92.5±20.2	0.20

* Plus–minus values are means ±SD. To convert the values for glucose to millimoles per liter, multiply by 0.055551. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. To convert the values for potassium to millimoles per liter, multiply by 0.2558. To convert the values for creatinine to micromoles per liter, multiply by 88.4. GFR denotes glomerular filtration rate, HDL high-density lipoprotein, and LDL low-density lipoprotein.

† Serious adverse events are events that are life-threatening, cause permanent disability, or necessitate hospitalization (see Section 7 in Supplementary Appendix 1).

‡ Symptoms were assessed at 12, 36, and 48 months after randomization in a random sample of 969 participants who were assessed for health-related quality of life.

§ Data are from the last visit at which assessments were made for each participant.

Table 3. Primary and Secondary Outcomes.

Outcome	Intensive Therapy (N=2363)		Standard Therapy (N=2371)		Hazard Ratio (95% CI)	P Value
	no. of events	*%/yr*	*no. of events*	*%/yr*		
Primary outcome*	208	1.87	237	2.09	0.88 (0.73–1.06)	0.20
Prespecified secondary outcomes						
Nonfatal myocardial infarction	126	1.13	146	1.28	0.87 (0.68–1.10)	0.25
Stroke						
Any	36	0.32	62	0.53	0.59 (0.39–0.89)	0.01
Nonfatal	34	0.30	55	0.47	0.63 (0.41–0.96)	0.03
Death						
From any cause	150	1.28	144	1.19	1.07 (0.85–1.35)	0.55
From cardiovascular cause	60	0.52	58	0.49	1.06 (0.74–1.52)	0.74
Primary outcome plus revascularization or nonfatal heart failure	521	5.10	551	5.31	0.95 (0.84–1.07)	0.40
Major coronary disease event†	253	2.31	270	2.41	0.94 (0.79–1.12)	0.50
Fatal or nonfatal heart failure	83	0.73	90	0.78	0.94 (0.70–1.26)	0.67

* The primary outcome was a composite of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes.

† Major coronary disease events, as defined in the protocol, included fatal coronary events, nonfatal myocardial infarction, and unstable angina.

the standard-therapy group (hazard ratio with intensive therapy, 1.07; 95% CI, 0.85 to 1.35; P=0.55). Rates of death from cardiovascular causes were 0.52% per year in the intensive-therapy group and 0.49% in the standard-therapy group (hazard ratio, 1.06; 95% CI, 0.74 to 1.52; P=0.74).

The two study groups did not differ significantly with respect to most of the other secondary outcomes. Nominally significant differences were seen in the rate of total stroke (0.32% per year in the intensive-therapy group vs. 0.53% per year in the standard-therapy group; hazard ratio, 0.59; 95% CI, 0.39 to 0.89; P=0.01) and in the rate of nonfatal stroke (0.30% per year in the intensive-therapy group vs. 0.47% per year in the standard-therapy group; hazard ratio, 0.63; 95% CI, 0.41 to 0.96; P=0.03). There were no significant interactions among prespecified subgroups (see Section 17 in Supplementary Appendix 1).

DISCUSSION

Intensive antihypertensive therapy in the ACCORD BP trial did not significantly reduce the primary cardiovascular outcome or the rate of death from any cause, despite the fact that there was a significant and sustained difference between the intensive-therapy group and the standard-therapy group in mean systolic blood pressure. There was also no significant benefit with respect to most of the secondary trial outcomes. At a significance level of less than 0.05, intensive blood-pressure management did reduce the rate of two closely correlated secondary outcomes — total stroke and nonfatal stroke. Assuming that this finding was real, the number needed to undergo intensive blood-pressure management to prevent one stroke over the course of 5 years was 89. These effects would be consistent with the findings of two meta-analyses of the effect of a reduction of 10 mm Hg in systolic blood pressure on the incidence of stroke[11,12]; the meta-analyses showed a relative risk with blood-pressure reduction of 0.64 with the use of data from observational studies and of 0.59 with the use of data from drug-treatment trials.[12]

The interpretation of the ACCORD BP results is complicated by the fact that the event rate observed in the standard-therapy group was almost 50% lower than the expected rate. This result may have been a consequence of the frequent use of statins and of inclusion criteria that di-

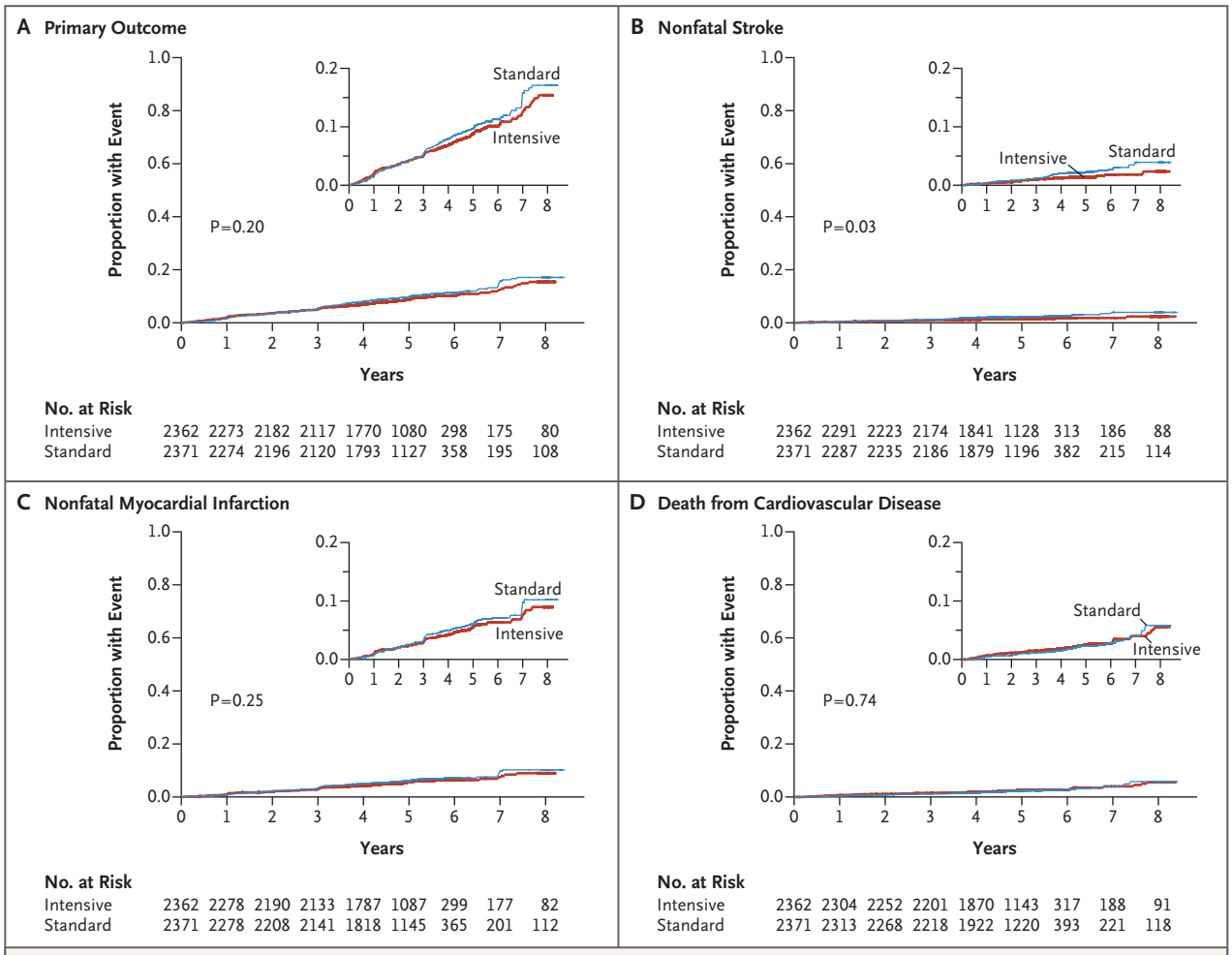


Figure 2. Kaplan–Meier Analyses of Selected Outcomes.

Shown are the proportions of patients with events for the primary composite outcome (Panel A) and for the individual components of the primary outcome (Panels B, C, and D). The insets show close-up versions of the graphs in each panel.

rected participants with dyslipidemia into the ACCORD lipid trial, leaving participants who were at lower risk in the blood-pressure trial.[5] The reduced power was reflected in the relatively wide confidence interval that does not exclude a 27% benefit for the primary end point.

There were some signals of possible harm associated with intensive blood-pressure control, including a rate of serious adverse events that was significantly higher in the intensive-therapy group than in the standard-therapy group. Both the estimated glomerular filtration rate and macroalbuminuria were reduced, but the implications of these changes on cardiovascular and renal outcomes are uncertain.

The United Kingdom Prospective Diabetes Study[13,14] and a post hoc subgroup analysis of the Hypertension Optimal Treatment (HOT) trial[15,16] showed reductions in cardiovascular events with antihypertensive therapy among patients with type 2 diabetes mellitus, but the participants in their intensively treated groups had much higher mean systolic blood-pressure levels (144 mm Hg in both cases) than did the participants in either group of our trial. In the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation trial (ADVANCE; ClinicalTrials.gov number, NCT00145925),[17] active treatment with an angiotensin-converting–enzyme inhibitor and a thiazide-type diuretic reduced the rate of death but did not significantly reduce a composite macrovascular outcome. How-

ever, the ADVANCE trial had no specified blood-pressure goals, and the mean systolic blood pressure in the intensive group (135 mm Hg) was not as low as the mean systolic blood pressure even in the ACCORD standard-therapy group. It is possible that lowering systolic blood pressure from the mid-130s to approximately 120 mm Hg does not further reduce most cardiovascular events or the rate of death, and most of the benefit from lowering blood pressure is achieved by targeting a goal of less than 140 mm Hg. Alternatively, it is possible that 5 years is not long enough to see significant cardiac benefits from the normalization of systolic blood pressure among persons with diabetes who have good control of glycemia, especially when other effective treatments, such as statins and aspirin, are used frequently.

There are several limitations of the ACCORD BP trial. First, the trial had an open-label design, a design that was not likely to have affected blood-pressure goals or measurement or the blinded ascertainment of the outcomes but may have affected the reporting of adverse events; second, the rate of cardiovascular events was lower than the expected rate in the standard-therapy group; and third, patients younger than 40 years of age were not included in the study and patients older than 79 years of age were not included after the vanguard phase. In addition, although it was not the intent of this trial to test the blood-pressure goal of 130 mm Hg that was recommended in the JNC 7 (a recommendation that was made after the ACCORD trial was initiated), it would be difficult to argue that such a target would be better than a target of 140 mm Hg, since even a blood-pressure goal of 120 mm Hg did not confer benefit.

In conclusion, the ACCORD BP trial evaluated the effect of targeting a systolic blood pressure of 120 mm Hg, as compared with a goal of 140 mm Hg, among patients with type 2 diabetes at high risk for cardiovascular events. The results provide no evidence that the strategy of intensive blood-pressure control reduces the rate of a composite of major cardiovascular events in such patients.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

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