Intensive Blood Pressure Treatment Does Not Improve Cardiovascular Outcomes in Centrally Obese Hypertensive Individuals With Diabetes

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Blood Pressure Trial

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OBJECTIVE—The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Blood Pressure Trial reported no differences in most cardiovascular disease (CVD) outcomes between intensive and standard blood pressure therapy in individuals with diabetes mellitus (DM) and hypertension. Many such individuals are centrally obese. Here we evaluate whether the trial outcomes varied by the level of central obesity.

RESEARCH DESIGN AND METHODS—The cohort included 4,687 people (47.7% women) with DM and hypertension. Mean age was 62.2, and mean follow-up was 4.7 years. Participants were randomly assigned to one of two blood pressure treatment strategies: intensive (systolic <120 mmHg) or standard (systolic <140 mmHg). Sex-specific quartiles of waist-to-height ratio were used as the measure of central obesity. The primary ACCORD outcome (a composite of nonfatal myocardial infarction [MI], nonfatal stroke, or CVD death) and three secondary outcomes (nonfatal MI, fatal or nonfatal stroke, and CVD death) were examined using proportional hazard models.

RESULTS—There was no evidence that the effect of intensively lowering blood pressure differed by quartile of waist-to-height ratio for any of the four outcomes ($P > 0.25$ in all cases). Controlling for waist-to-height quartile had no significant impact on previously published results for intensive blood pressure therapy. Waist-to-height ratio was significantly related to CVD mortality (hazard ratio 2.32 [95% CI 1.40–3.83], $P = 0.0009$ comparing the heaviest to lightest quartiles), but not to the other outcomes ($P > 0.09$ in all cases).

CONCLUSIONS—Intensive lowering of blood pressure versus standard treatment does not ameliorate CVD risk in individuals with DM and hypertension. These results did not vary by quartile of waist-to-height ratio.

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Central obesity is strongly and linearly related to the development of hypertension (1). The mechanisms for this association lie in the relationship of visceral fat with cardiometabolic disturbances, such as insulin resistance, increased sympathetic tone, inflammatory protein production, intravascular volume expansion, and activation of the renin-angiotensin system (2). Many of these factors also lead to the development of diabetes mellitus (DM).

In general, greater relative cardiovascular disease (CVD) risk reduction is obtained from risk factor modification in individuals who are "sickest." For example, individuals with DM, compared with those without DM, have greater risk reduction of myocardial infarction (MI) and stroke from blood pressure reduction (3). It is therefore intuitive to hypothesize (although not necessarily true) that aggressive modification of hypertension in centrally obese individuals with DM could lead to greater CVD event reduction relative to those with DM who are not centrally obese. This hypothesis has not been tested.

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Blood Pressure Trial tested the hypothesis that intensive lowering of systolic blood pressure (<120 mmHg) in individuals with type 2 DM and hypertension would result in fewer adverse CVD outcomes than conventional treatment (<140 mmHg). The study reported that intensive lowering of blood pressure did not reduce the primary composite outcome of cardiovascular death, nonfatal MI, or nonfatal stroke or secondary outcomes, with the exception of stroke (4). In this study, we examine whether central obesity modifies the risk of CVD outcomes in those randomized to intensive versus standard blood pressure treatment. We hypothesize that intensive blood pressure modification results in greater CVD

risk reduction in those with higher versus lower degrees central obesity.

RESEARCH DESIGN AND METHODS

—ACCORD was a randomized trial that enrolled 10,251 high-risk participants with type 2 DM (5,6). All participants were randomly assigned to intensive (HbA_{1c} <6%) or standard glycemic control (HbA_{1c} 7.0–7.9%). These participants were also assigned to a lipid or a blood pressure substudy. For the lipid substudy, 5,518 were assigned in a 2 × 2 factorial design to simvastatin plus placebo or simvastatin plus fenofibrate. This substudy tested the hypothesis that lowering triglycerides and raising HDL cholesterol on the background of an LDL level of less than 100 mg/dL improves CVD outcomes.

The remaining 4,733 participants were assigned to the blood pressure substudy in a 2 × 2 factorial design (the ACCORD Blood Pressure Trial). Participants with a systolic blood pressure of 130–180 mmHg who were taking three or fewer antihypertensive medications and who had less than 1.0 g protein excretion in a 24-h urine collection were eligible for the blood pressure trial. These participants were randomly assigned to one of two treatment strategies: intensive, systolic blood pressure (<120 mmHg) or standard (<140 mmHg).

Details of study visit schedules, treatment strategies for achieving goal blood pressure values in each arm, and laboratory methods have been published (7). The primary outcome for the study was the time to the first occurrence of a major cardiovascular event, which was defined as the composite of nonfatal MI, nonfatal stroke, or CVD death. Prespecified secondary outcomes included nonfatal MI, fatal and nonfatal stroke, and death from CVD. All participants signed informed consent upon entry into the main ACCORD trial.

Waist circumference was measured at the baseline visit with a tape measure to the nearest centimeter at the level of the iliac crest. Hip circumference was not measured in ACCORD, so the waist-to-hip ratio (the traditional test of central obesity) was not available. In its place, we used the waist circumference-to-height ratio, which has been validated as a marker of CVD outcomes related to central obesity (8). A waist-to-height ratio of less than 50% is estimated to be associated with less CVD risk than one above this level.

Statistical methods

Continuous variables are reported as mean (SD) or as the median (interquartile range) for highly skewed distributions. Discrete variables are reported as the number (percent) possessing the characteristic. Changes were calculated for waist, height, waist-to-height ratio, weight, systolic and diastolic blood pressures, and estimated glomerular filtration rate by the Modification of Diet in Renal Disease formula as the difference between baseline and the last available measurement for each participant.

The primary results for the ACCORD Blood Pressure Trial previously have been presented based on proportional hazards models that included terms for intensive versus standard blood pressure group assignment, intensive versus standard glycemia group assignment, CVD history, and for the primary outcome only, clinical center network (4). Here, these models are extended by adding a term for sex-specific

Table 1—*Characteristics of ACCORD Blood Pressure Trial participants at baseline*

Characteristic	Intensive therapy *n* = 2,341	Standard therapy *n* = 2,346
Age (years)	62.19 (6.8)	62.25 (6.93)
Female sex	1,117 (47.71%)	1,118 (47.66%)
Intensive glycemic treatment	1,167 (49.85%)	1,179 (50.26%)
Race or ethnic group		
Non-Hispanic white	1,440 (61.51%)	1,394 (59.42%)
Black	555 (23.71%)	573 (24.42%)
Hispanic	159 (6.79%)	169 (7.2%)
Education		
Less than high school	401/2,338 (17.15%)	366/2,345 (15.61%)
High school graduate or GED	603/2,338 (25.79%)	653/2,345 (27.85%)
Some college	764/2,338 (32.68%)	747/2,345 (31.86%)
College degree or higher	570/2,338 (24.38%)	579/2,345 (24.69%)
Previous cardiovascular event	796 (34%)	782 (33.33%)
Previous heart failure	109/2,317 (4.7%)	94/2,321 (4.05%)
Cigarette smoking		
Never	1,043/2,338 (44.61%)	1,055/2,345 (44.99%)
Former	984/2,338 (42.09%)	981/2,345 (41.83%)
Current	311/2,338 (13.3%)	309/2,345 (13.18%)
Weight (kg)	92.07 (19.4)	91.84 (17.7)
BMI (kg/m^2)	32.17 (5.69)	32.09 (5.45)
Waist (cm)	106.04 (14.30)	105.34 (13.50)
Height (cm)	168.92 (10.19)	169.06 (9.85)
Blood pressure (mmHg)		
Systolic	139.03 (16.12)	139.38 (15.49)
Diastolic	75.95 (10.58)	75.99 (10.2)
Diabetes duration (years)	9 (5–15)	10 (5–15)
Glycated hemoglobin (%)	8.36 (1.09)	8.3 (1.08)
Fasting plasma glucose (mmol/L)	9.77 (3.20)	9.61 (3.20)
Cholesterol (mmol/L)		
Total	5.02 (1.17)	4.96 (1.15)
LDL	2.88 (0.97)	2.82 (0.93)
HDL		
Women	1.33 (0.37)	1.33 (0.35)
Men	1.09 (0.32)	1.07 (0.29)
Plasma triglycerides (mmol/L)	1.66 (1.11–2.57)	1.66 (1.11–2.53)
Potassium (mmol/L)	4.47 (0.47)	4.48 (0.84)
Serum creatinine (mmol/L)	79.56 (21.22)	79.56 (21.22)
eGFR ($mL/min/1.73\ m^2$)	91.57 (30.32)	91.69 (27.18)
Urinary albumin-to-creatinine ratio	1.64 (0.79–4.94)	1.57 (0.78–5.14)

Continuous data are shown as mean (SD) or median (interquartile range). eGFR, estimated glomerular filtration rate; GED, general equivalency diploma. Conversion factors for obtaining conventional units: glucose, divide by 0.0555 for mg/mL; creatinine, divide by 88.4 for mg/dL; triglycerides, divide by 0.0113 for mg/dL; cholesterol, divide by 0.0259 for mg/dL; ratio albumin (mg) to creatinine (mmol/L), divide by 0.113 for mg/g.

Table 2—*Change from baseline to exit visit*

	Intensive therapy *n* = 2,341	Standard therapy *n* = 2,346
Waist-to-height ratio		
n	1,862	1,890
Mean (SD)	0 (1)	−0.02 (1)
Waist (cm)		
n	1,875	1,897
Mean (SD)	1.32 (15)	1.22 (13)
Height (cm)		
n	1,885	1,922
Mean (SD)	−0.76 (17)	−0.42 (38)
Weight (kg)		
n	1,905	1,933
Mean (SD)	1.06 (10)	0.67 (10)
Blood pressure (mmHg)		
Systolic		
n	1,905	1,937
Mean (SD)	−17.77 (20)	−5.59 (19)
Diastolic		
n	1,905	1,937
Mean (SD)	−11.34 (11)	−5.97 (11)
eGFR (mL/min/1.73m^2)		
n	1,991	2,017
Mean (SD)	−16.6 (23)	−11.32 (24)

eGFR, estimated glomerular filtration rate.

waist-to-height quartile (marginal model). We also added terms representing a blood pressure treatment group by waist-to-height quartile interaction (full model) to test whether effects of treatment varied across quartiles of central obesity. Waist-to-height quartiles were fit both as a single linear covariate to provide a linear trend test and through the use of indicator variables. As a sensitivity analysis, we also repeated the analysis using quartiles of waist circumference. Two-tailed *P* values for these analyses were based on likelihood ratio tests calculated from the proportional hazards models. Event rates were calculated, incorporating the censored data, as the number of events per follow-up year.

Given the post hoc nature of these analyses, no adjustments for multiple comparisons were performed. If our four outcomes were independent, the probability of making at least one type I error would be $[1 - (1 - 0.05)^4] = 0.19$. All analyses assumed data were missing at random and were performed under the intent-to-treat principle, analyzing participants according to their original group assignments regardless of adherence. Similar analyses were performed for each of the three components of the primary outcome. All analyses were done using SAS 9.2 software (SAS Institute, Cary, NC)

RESULTS—Of the 4,733 participants in the ACCORD Blood Pressure Trial, 46 did not have baseline waist-to-height ratio data, leaving 4,687 participants for analysis. The distribution of waist-to-height ratios, categorized by sex, is presented in Supplementary Table 1. The mean and median waist-to-height ratios exceeded 0.60, indicating an obese sample. Women had higher ratios than men.

The distribution of baseline covariates, categorized by intensive versus standard blood pressure randomization, is reported in Table 1. The groups were balanced in sex, ethnicity, education, prior CVD disease, smoking status, BMI, baseline blood pressure, HbA_{1c}, lipid, and renal values. Changes in CVD risk factors during follow-up are presented in Table 2. Changes were balanced between the two treatment approaches, other than the changes in blood pressure levels, which was the intent of the study, and in renal function, where there was more decline in the standard group.

A forest plot showing intensive versus standard blood pressure group event rates and hazard ratios (HRs) by waist-to-height quartiles is presented in Fig. 1. These HRs, 95% CIs, and interaction *P* values are estimated from the full model using indicator variables to account for waist-to-height quartiles. Although a trend toward greater benefit of intensive treatment among participants with higher waist-to-height ratios was apparent for some outcomes, differences in HRs between quartiles did not achieve statistical significance for any of the four outcomes ($P > 0.24$ for all four tests of interaction). Similar results were obtained when waist-to-height quartile was modeled as single linear covariate ($P > 0.25$ for all four tests of interaction).

Results from marginal models controlling for blood pressure group assignment and waist-to-height quartile fit a single linear covariate (Table 3). After controlling for waist-to-height quartile, the effects of blood pressure treatment group assignment are generally similar with those previously described (4), with evidence ($P = 0.022$) of an effect of intensive blood pressure lowering on total stroke but not for the primary outcome, nonfatal MI or CVD mortality ($P \geq 0.23$ for all three outcomes). There was evidence that a higher waist-to-height quartile was related to an increased risk of CVD mortality (HR 2.32, $P = 0.0009$ comparing the 4th to 1st quartile), but not for other outcomes ($P > 0.09$ in for all three cases). There was no evidence of departure from linearity for waist-to-height quartiles among any of the outcomes ($P > 0.17$ in all cases). Qualitatively similar results were obtained when using waist circumference quartile as a measure of central obesity (data not shown).

CONCLUSIONS—Contrary to our hypothesis, a participant's baseline waist-to-height ratio did not modify the risk of CVD outcomes in individuals with DM whose blood pressure was treated to <120 mmHg versus <140 mmHg. The results are consistent with those of the parent ACCORD Blood Pressure Trial, which showed no benefit for intensive versus standard blood pressure lowering in people with DM, other than for stroke prevention. Recommendations from the American Heart Association and the American Stroke Association (9,10) are careful to point out that there is increased risk of CVD with increasing adiposity and blood pressure, but there are no clear guidelines for the amount that blood pressure should be lowered. There are also no clear data to suggest that lowering blood pressure in the setting of obesity

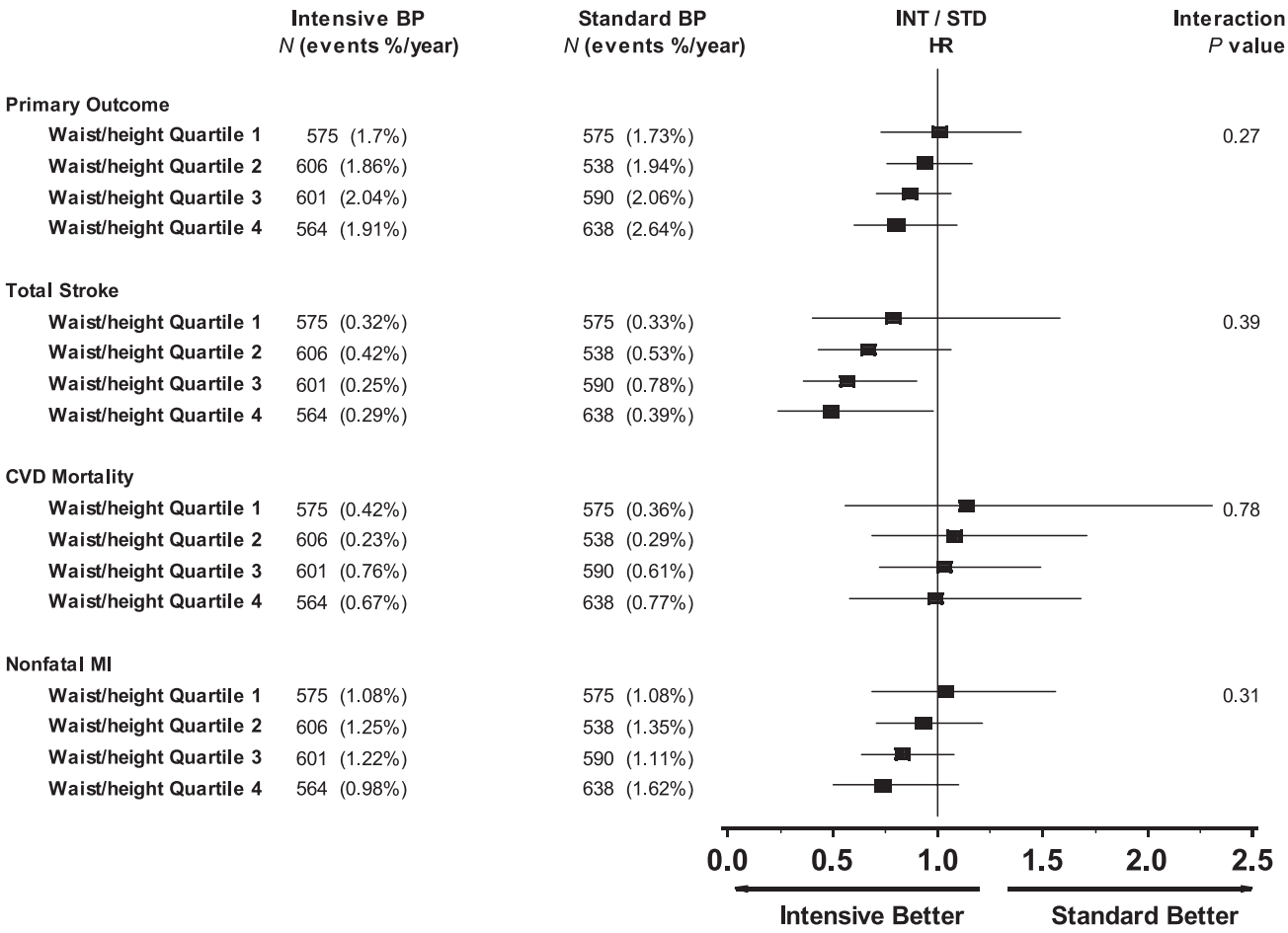

Figure 1—*Comparison of CVD outcomes by level of central obesity in the ACCORD Blood Pressure Trial. BP, blood pressure; INT, intensive; STD, standard.*

is a useful means for CVD prevention. Given the increasing number of centrally obese hypertensive diabetic persons in the U.S. population, our findings are of clinical importance. Of further note, the INTERHEART study from 52 countries (11) showed that measures of central obesity (compared with BMI) increase the proportion of individuals classified as obese. This is especially so in parts of the world not considered to have high rates of obesity, such as the Middle East, south Asia, and southeast Asia. Our results therefore are broadly applicable.

It may be asked why intensively lowering hypertensive blood pressure levels did not offer a benefit compared with standard blood pressure lowering for preventing CVD in participants who were centrally obesity. One explanation is that in a population with DM and hypertension, in which insulin resistance and its associated risk factors are present in each quartile of waist-to-height ratio, the degree of central obesity per se is not independently related to CVD risk. Indeed, the presence of DM and hypertension in individuals without a marked degree of central obesity suggests that such individuals are as sick, or sicker, than those with more central obesity.

A noteworthy finding is that central obesity was associated with increased CVD mortality but not with other CVD end points. Three prospective studies of diabetic participants have also reported such an association (12–14). However, we did not find an association of waist-to-height ratio with other CVD end points. This is surprising, because morbidity outcomes share similar pathomechanisms with mortality outcomes. Our finding, however, is in keeping with some other studies. In a report from the Emerging Risk Factors Collaboration (15), a meta-analysis of 102 prospective studies of fasting glucose levels, DM, and risk of vascular disease, DM was one-third more strongly related to fatal than to nonfatal MI. The

Table 3—*HRs for study outcomes categorized by treatment group across quartiles of waist-to-height ratios and tests for trend*

	Blood pressure intervention		Waist-to-height quartile	
Outcome	HR (95% CI)	*P*	HR (95% CI)	*P*
Primary	0.89 (0.74–1.08)	0.23	1.24 (0.97–1.61)	0.09
Total stroke	0.62 (0.41–0.94)	0.022	1.03 (0.86–1.23)	0.76
CVD mortality	1.04 (0.72–1.49)	0.83	2.32 (1.40–3.83)	0.0009
Nonfatal MI	0.88 (0.69–1.11)	0.27	1.03 (0.92–1.14)	0.62

Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) (16) reported that increased levels of inflammation factors are more strongly associated with fatal than with nonfatal CVD events. Greater degrees of central obesity are related to increased inflammation levels.

We used the waist-to-height ratio as our measure of central obesity. Waist-to-height ratios have recently become more widely used for this purpose and have been shown to discriminate as well or better than waist-to-hip ratios for the prediction of CVD risk in people with DM (10,13). More important, this measure avoids the effect of sarcopenia that develops in the hips with aging, which may exaggerate the effect of the waist-to-hip ratio on CVD outcomes.

Strengths of this study include its rigorous study design and data acquisition, complete follow-up information, racial diversity, and the novel question it addressed. A limitation should be noted beyond its post hoc nature. The study had a modest number of outcomes, and follow-up was short. This was partly due to the lower-than-expected rate of CVD outcomes in the main ACCORD trial; hence, the power to detect significant differences by the degree of central obesity was limited. With longer follow-up and more events, statistical significance could possibly be achieved for several outcomes.

In conclusion, the degree of central obesity did not modify the treatment effect noted in the ACCORD Blood Pressure Trial. Aggressively lowering blood pressure levels in centrally obese individuals with hypertension and DM is no more effective than standard blood pressure reduction for prevention of CVD outcomes except for stroke.

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J.I.B. collected data for the study, helped with analyses, and wrote the manuscript. A.G.H. performed statistical analysis. G.W.E. performed statistical analysis and contributed to discussion. J.L.F. edited the manuscript for intellectual content and contributed to discussion. R.M.C., G.L.B, A.R.K, and C.F.P. collected data for the study and edited the manuscript for intellectual content. W.C.C. was lead to the ACCORD Blood Pressure Trial, collected data for the study, and edited the manuscript for intellectual content. J.I.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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