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Tight Blood Pressure Control and Cardiovascular Outcomes Among Hypertensive Patients With Diabetes and Coronary Artery Disease

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Context Hypertension guidelines advocate treating systolic blood pressure (BP) to less than 130 mm Hg for patients with diabetes mellitus; however, data are lacking for the growing population who also have coronary artery disease (CAD).

Objective To determine the association of systolic BP control achieved and adverse cardiovascular outcomes in a cohort of patients with diabetes and CAD.

Design, Setting, and Patients Observational subgroup analysis of 6400 of the 22 576 participants in the International Verapamil SR-Trandolapril Study (INVEST). For this analysis, participants were at least 50 years old and had diabetes and CAD. Participants were recruited between September 1997 and December 2000 from 862 sites in 14 countries and were followed up through March 2003 with an extended follow-up through August 2008 through the National Death Index for US participants.

Intervention Patients received first-line treatment of either a calcium antagonist or β-blocker followed by angiotensin-converting enzyme inhibitor, a diuretic, or both to achieve systolic BP of less than 130 and diastolic BP of less than 85 mm Hg. Patients were categorized as having tight control if they could maintain their systolic BP at less than 130 mm Hg; usual control if it ranged from 130 mm Hg to less than 140 mm Hg; and uncontrolled if it was 140 mm Hg or higher.

Main Outcome Measures Adverse cardiovascular outcomes, including the primary outcomes which was the first occurrence of all-cause death, nonfatal myocardial infarction, or nonfatal stroke.

Results During 16 893 patient-years of follow-up, 286 patients (12.7%) who maintained tight control, 249 (12.6%) who had usual control, and 431 (19.8%) who had uncontrolled systolic BP experienced a primary outcome event. Patients in the usual-control group had a cardiovascular event rate of 12.6% vs a 19.8% event rate for those in the uncontrolled group (adjusted hazard ratio [HR], 1.46; 95% confidence interval [CI], 1.25-1.71; $P<.001$). However, little difference existed between those with usual control and those with tight control. Their respective event rates were 12.6% vs 12.7% (adjusted HR, 1.11; 95% CI, 0.93-1.32; $P=.24$). The all-cause mortality rate was 11.0% in the tight-control group vs 10.2% in the usual-control group (adjusted HR, 1.20; 95% CI, 0.99-1.45; $P=.06$); however, when extended follow-up was included, risk of all-cause mortality was 22.8% in the tight control vs 21.8% in the usual control group (adjusted HR, 1.15; 95% CI, 1.01-1.32; $P=.04$).

Conclusion Tight control of systolic BP among patients with diabetes and CAD was not associated with improved cardiovascular outcomes compared with usual control.

Trial Registration clinicaltrials.gov Identifier: NCT00133692

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The 1984 report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recognized that patients with diabetes mellitus represented a special population.[1] In 1993, the fifth report of the Joint National Committee recommended that the treatment goal for patients with diabetes should reduce blood pressure (BP) to less than 130/85 mm Hg.[2] This lower goal was based primarily on data from the 1501-patient cohort with diabetes enrolled in the Hypertension Optimal Treatment (HOT) trial,[3] which suggested reduced cardiovascular outcomes for 501 patients assigned to a diastolic treatment goal of less than 80 mm Hg compared with those assigned to treatment goals that allowed for higher BP. Data from the United Kingdom Prospective Diabetes Study (UKPDS) group[4,5] showed that patients with diabetes and hypertension assigned to a tight BP goal group had reduced macrovascular and microvascular outcomes. In 2002, the American Diabetes Association recommended that the BP treatment goal for patients with diabetes should be less than 130/80 mm Hg, which it reaffirmed in 2010.[6-8]

In keeping with epidemiological data suggesting that there is no evidence of a threshold on adverse outcomes for BP

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to approximately 115/75 mm Hg,[9] the American Diabetes Association concluded that "there is no threshold value for BP, and risk continues to decrease well into the normal range."[10] In 2003, the seventh report of the Joint National Committee[11] and guidelines from many other national and international societies[12] confirmed the lower BP treatment goal of less than 130/80 mm Hg for patients with diabetes, and in 2007 the American Heart Association Scientific Statement recommended that this lower BP treatment goal be expanded to include patients with coronary artery disease (CAD), stable or unstable angina, and myocardial infarction with or without ST elevation.[13]

A recent study involving patients without diabetes but who had hypertension reported that patients randomly assigned to a tight-control BP (systolic BP <130 mm Hg) treatment group had a significantly lower prevalence of left ventricular hypertrophy, an intermediate outcome known to be a strong predictor of cardiovascular outcomes, and had a significantly reduced risk of a secondary outcome, which included cardiovascular morbidity or all-cause mortality.[14] However, other studies[15-18] involving patients with hypertension and CAD reported a J-shaped relationship between BP and cardiovascular morbidity and mortality, which has been attributed primarily to associated health conditions and not to specific antihypertensive treatment. Importantly, among patients with diabetes, hypertension, and CAD, we reported a significant increase in cardiovascular risk among those who achieved a systolic BP of 110 mm Hg or lower,[19] questioning the notion that there is no threshold for BP lowering recently espoused by the American Diabetes Association, American Heart Association, and others.

Data from the HOT trial[3] were used to support the current recommendation for a lower diastolic BP goal for patients with diabetes. However, there are limited data about patients with diabetes to support such a recommendation for lower systolic BP,[11,20] particularly in the growing population of those with CAD.[8] Accordingly, we investigated systolic BP achieved and cardiovascular outcomes among participants in the International Verapamil SR-Trandolapril Study (INVEST) who had hypertension, diabetes, and CAD. Based on current guideline recommendations, we hypothesized that patients with diabetes who achieved systolic BP of less than 130 mm Hg would have reduced risk of cardiovascular events compared with those who managed to keep their systolic BP within the range of at least 130 mm Hg to less than 140 mm Hg.

METHODS

Study Design

This is an observational, secondary analysis derived from INVEST, which was a prospective, randomized trial comparing clinical outcomes of 22 576 patients with hypertension and CAD enrolled between September and December 2000 and followed up through March of 2003. Inclusion and exclusion criteria, study design details, and full results have been published.[21,22] Briefly, after undergoing an extensive cardiovascular history and physical examination, clinically stable patients were randomly assigned to receive either a calcium antagonist–based or β-blocker–based antihypertensive treatment strategy. The calcium antagonist–based strategy consisted of initiation with verapamil sustained release, followed by the addition of the angiotensin-converting enzyme inhibitor trandolapril as second-line therapy and hydrochlorothiazide added as third-line therapy. The β-blocker–based strategy consisted of initiation with atenolol, followed by the addition of hydrochlorothiazide as second-line therapy, and the addition of trandolapril as third-line therapy. For patients with diabetes at the time of enrollment, trandolapril was recommended as part of initial therapy, regardless of treatment strategy assignment. Patients were evaluated every 6 weeks for the first 6 months and then biannually for at least 2 years to assess BP, adherence to medication, and adverse cardiovascular outcomes. The protocol was conducted in accordance with principles outlined in the Declaration of Helsinki, and institutional review boards and ethics committees at participating sites approved the protocol. Patients provided written informed consent. Overall, the strategies were equivalent in preventing all-cause death, nonfatal myocardial infarction, or nonfatal stroke. The primary outcome was the first occurrence of all-cause death, nonfatal myocardial infarction, or nonfatal stroke. The secondary outcomes included all-cause death, nonfatal MI, and nonfatal stroke individually.[22]

A total of 6400 patients (28%) had diabetes at baseline (defined by a history of physician-diagnosed diabetes, use of oral hypoglycemic medication or insulin, or both). Because race/ethnicity is known to influence cardiovascular outcomes, data were collected to characterize race/ethnicity based on patient report with interaction by site investigator, choosing all that were applicable among the following options: white, black, Asian, Hispanic, or other. We have previously published the characteristics and outcomes concerning this cohort according to treatment strategy and found no significant differences comparing the 2 treatment strategies.[19] The current analysis was designed to investigate the effects of systolic BP achieved on risk of cardiovascular events in the cohort with diabetes during protocol-specified follow-up. To further assess the long-term cumulative effect on all-cause mortality, we searched the National Death Index for patients with diabetes who were enrolled in participating US sites up to 5 years after study follow-up. To be considered a confirmed death, we required 4 of 5 matches among the following: name, Social Security number, date of birth, city, and state.

Statistical Analysis

Patients were categorized into 3 groups by their average systolic BP while taking study medication: tight control, less than 130 mm Hg; usual control, 130 mm Hg to less than 140 mm Hg; or un-

controlled, 140 mm Hg or higher. Baseline characteristics of these 3 BP groups were compared using analysis of variance for continuous variables and the χ^2 test for categorical variables. Average systolic BP was calculated for each patient using all but their baseline BP measurements until they died, experienced nonfatal myocardial infarction or nonfatal stroke, or were censored. All patients had at least 1 available BP measurement. For analyses performed during follow-up, patients who did not experience any component of the primary outcome were censored at the last study visit. For the extended follow-up analysis, patients who did not appear in the National Death Index were censored on the day the death index search was completed. Outcomes were assessed with Kaplan-Meier plots, and a stepwise Cox proportional hazard regression model was used to evaluate the role of systolic BP on risk of the primary outcome with the usual-control group as the reference. To better understand risk of very low systolic BP among patients in the tight-control group, we further categorized systolic BP of less than 130 mm Hg in 5-mm Hg segments. A stepwise Cox proportional hazard regression model was used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for risk of all-cause mortality (125 mm Hg to <130 mm Hg as the reference). Prespecified covariates forced into the models included treatment strategy, age in decades, race/ethnicity, sex, history of prior myocardial infarction, and heart failure. Other baseline covariates were selected for entry in the model on the basis of a *P* value of .20 or less and were retained in the model for a *P* value of .05 or less. To test the validity of the findings, several sensitivity analyses were performed, including removal of patients with heart failure, removal of BP measurements obtained during the first 6 months of the study, evaluation of outcomes at the 6-month and 1-year time points, and inclusion of terms for baseline systolic BP and change in systolic BP in a Cox proportional hazard regression model.

The overall significance level for the study was $P < .05$ using a 2-sided test. At an α level of .05, there was greater than 80% power to detect an HR of 1.12 or greater. All analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina).

RESULTS

Baseline Characteristics and BP Control

Of the 22 576 INVEST participants, 6400 had diabetes at the time of enrollment. Their mean age was 66 years, 54% were women, and they had a mean body mass index of 30, calculated as weight in kilograms divided by height in meters squared (TABLE 1). Patients were followed up over a total of 16 893 patient-years, and 35.2% were observed to have tight control; 30.8%, usual control; and 34%, uncontrolled systolic BP.

Analysis According to BP Achieved

In accordance with our previous analysis,[19] there was no difference comparing treatment strategies with regard to BP lowering in any of the groups. Mean (SD) systolic BP reduction at 24 months

Table 1. Baseline Characteristics of Patients According to Systolic Blood Pressure While Taking Medication

	No. (%) of Patients, Systolic Blood Pressure Control			
	Tight (n = 2255)	Usual (n = 1970)	Uncontrolled (n = 2175)	*P* Value
Age, mean (SD), y	65 (9)	66 (9)	67 (9)	<.001
>70 y	641 (28)	629 (32)	784 (36)	<.001
BMI, mean (SD)	30 (6.0)	31 (6.0)	31 (6.0)	<.001
Blood pressure, mean (SD), mm Hg				
Systolic	144 (19)	149 (17)	159 (19)	<.001
Diastolic	85 (12)	85 (12)	86 (12)	<.001
Heart rate, mean (SD), beats/min	77 (10)	77 (9)	77 (10)	.38
β-Blocker strategy	1129 (50)	996 (49)	1136 (52)	.11
Women	1116 (49)	1065 (54)	1274 (59)	<.001
Race/ethnicity				
White	896 (40)	902 (46)	996 (46)	<.001
Black	210 (9.3)	299 (15)	490 (23)	
Hispanic	1086 (48)	733 (37)	612 (28)	
Other/multiracial	63 (2.8)	36 (2.0)	77 (3.5)	
Prior MI	797 (35)	645 (33)	735 (34)	.19
Prior stroke/TIA	184 (8.2)	168 (8.5)	236 (11)	.004
LVH	596 (26)	437 (22)	522 (24)	.004
Heart failure (New York Heart Association class I-III)	199 (8.8)	134 (6.8)	188 (8.6)	.03
PAD	424 (19)	326 (17)	366 (17)	.10
Smoking history	1080 (48)	883 (45)	957 (44)	.02
Renal impairment[a]	79 (3.5)	47 (2.4)	108 (5.0)	<.001
Hypercholesterolemia[b]	1413 (63)	1221 (62)	1318 (61)	.34
Cancer	81 (3.6)	60 (3.1)	74 (3.4)	.61
Medication use				
Lipid lowering	989 (44)	846 (43)	856 (39)	.006
Aspirin or other antiplatelet	1386 (61)	1150 (58)	1264 (58)	.04
NSAID	442 (20)	398 (20)	414 (19)	.64
Use of any antihypertensives	2052 (91)	1786 (91)	1957 (90)	.50

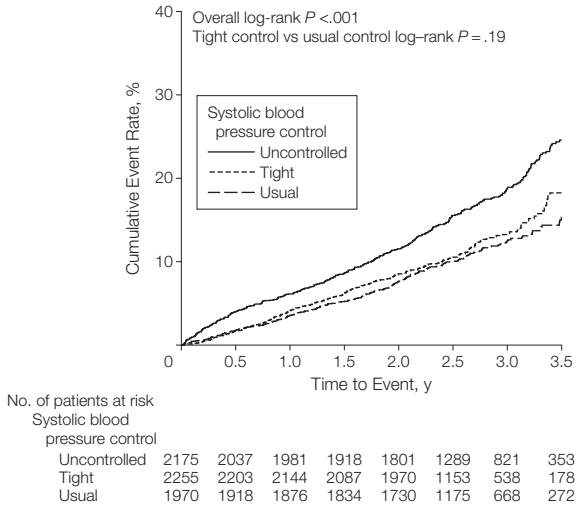
Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; LVH, left ventricular hypertrophy; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; PAD, peripheral arterial disease; TIA, transient ischemic attack.
[a] History of, or currently elevated serum creatinine level but less than 4 mg/dL (to convert from mg/dL to μmol/L, multiply by 88.4).
[b] History of, or currently taking lipid-lowering medications.

Table 2. Primary and Secondary Outcomes

	Systolic Blood Pressure Control											
	Tight (n = 2255)				Usual (n = 1970)				Uncontrolled (n = 2175)			
Outcome	No. of Events	% (95% CI)	Total Years of Follow-up	Event Rate Per 100 Patient-Years	No. of Events	% (95% CI)	Total Years of Follow-up	Event Rate Per 100 Patient-Years	No. of Events	% (95% CI)	Total Years of Follow-up	Event Rate Per 100 Patient-Years	*P* Value[a]
Primary outcome[b]	286	12.7 (11.3-14.1)	5741	4.98	249	12.6 (11.2-14.1)	5339	4.66	431	19.8 (18.1-21.5)	5775	7.46	<.001
All-cause mortality	248	11.0 (9.7-12.3)	5811	4.27	201	10.2 (8.9-11.5)	5423	3.71	334	15.4 (13.8-16.9)	5975	5.59	<.001
Nonfatal MI	29	1.3 (0.8-1.8)	5782	0.5	33	1.7 (1.1-2.2)	5380	0.61	67	3.1 (2.4-3.8)	5866	1.14	.008
Nonfatal stroke	22	1.0 (0.6-1.4)	5786	0.38	26	1.3 (0.8-1.8)	5382	0.48	52	2.4 (1.7-3.0)	5875	0.89	.001
Total MI	108	4.8 (3.9-5.7)	5782	1.87	100	5.1 (4.1-6.0)	5380	1.86	185	8.5 (7.3-9.7)	5865	3.15	<.001
Total stroke	34	1.5 (1.0-2.0)	5786	0.59	33	1.7 (1.1-2.2)	5384	0.61	70	3.2 (2.5-4.0)	5875	1.19	<.001

Abbreviation: CI, confidence interval; MI, myocardial infarction.
[a] *P* value for comparison of event rate per 100 patient-years, between systolic blood pressure categories.
[b] *Primary outcome* is defined as the first occurrence of all-cause death, nonfatal MI, or nonfatal stroke.

Figure 1. Cumulative Event Rate for Primary Outcome



Primary outcomes are a composite of the first occurrence of all-cause death, nonfatal myocardial infarction, or nonfatal stroke.

was 22.5 (20.7) mm Hg in the tight-control, 17.8 (20.8) mm Hg in the usual-control, and 12.9 (26.4) mm Hg in the uncontrolled groups.

Treatment

Mean daily doses for all 4 study drugs were lowest in the tight-control group (verapamil SR, 274 mg/d; atenolol, 69 mg/d; trandolapril, 3.4 mg/d; and hydrochlorothiazide, 28 mg/d) and highest in the uncontrolled group (verapamil SR, 345 mg/d; atenolol, 96 mg/d; trandolapril, 4.6 mg/d; and hydrochlorothiazide, 33 mg/d). Half the patients in the tight-control group were taking 3 or more antihypertensive drugs, whereas more than two-thirds of patients in the usual-control and uncontrolled groups were taking 3 or more antihypertensive agents. Importantly, 75% or more of patients in all 3 groups were taking a renin angiotensin-system blocking agent.

Primary and Secondary Outcomes

The primary outcome occurred in 12.7% of those in the tight-control group (adjusted HR, 1.11; 95% CI, 0.93-1.32), 12.6% of the usual-control group (reference), and 19.8% of the uncontrolled groups (adjusted HR, 1.46; 95% CI, 1.25-1.71; *P* value for trend, <.001). TABLE 2 summarizes incidence and rate of the primary and secondary outcomes by group. Supporting our prior analysis,[19] there was no significant difference in occurrence of the primary outcome in any of the groups by treatment strategies using the atenolol strategy as the reference. The HR for the tight-control group was 0.92 (95% CI, 0.73-1.16; *P*=.46); for the usual-control group, 1.05 (95% CI, 0.82-1.35; *P*=.69); and for the uncontrolled group, 1.14 (95% CI, 0.94-1.38; *P*=.18).

The primary and secondary outcomes, including nonfatal myocardial infarction, nonfatal stroke, and all-cause mortality, were significantly different comparing the 3 groups (FIGURE 1 and FIGURE 2). For all-cause mortality, there was a significant increase in risk for the tight-control group compared with the usual-control group (log-rank *P*=.04; Figure 2). After adjustment for baseline differences, the risk remained elevated, although not statistically significant (11.0% for the tight-control group vs 10.2% for the usual-control group; adjusted HR, 1.20; 95% CI, 0.99-1.45; *P*=.06). The extended follow-up analysis for all-cause mortality in the US cohort showed that a total of 841 deaths had occurred in the 5 years immediately following the close of

INVEST. Two hundred forty-four patients died in the tight-control group; 248 in the usual control group; and 349 in the uncontrolled group. When evaluating all-cause mortality for the entire follow-up period, risk was not significantly different comparing the tight- and usual-control groups (log-rank $P=.06$; Figure 2), but after adjustment, risk of all-cause mortality was significantly greater in the tight-control group (22.8%) than in the usual-control group (21.8%; adjusted HR, 1.15; 95% CI, 1.01-1.32; $P=.04$).

All of the sensitivity analyses performed confirmed our overall observation of no difference in risk of the primary and all-cause mortality outcomes comparing the tight- and usual-control groups. After exclusion of the 521 patients with heart failure at baseline, the adjusted HR for the primary outcome was 1.07 (95% CI, 0.89-1.29; $P=.48$); for all-cause mortality, 1.17 (95% CI, 0.95-1.44; $P=.15$). After excluding the first 6 months of BP measurements, when BP was most variable, the adjusted HR for the primary outcome was 1.16 (95% CI, 0.95-1.41; $P=.16$); for all-cause mortality, 1.25 (95% CI, 1.00-1.55; $P=.05$). Evaluation of outcomes during the first 6 months of follow-up resulted in an adjusted HR of 0.92 (95% CI, 0.58-1.45; $P=.70$) for the primary outcome and 0.95 (95% CI, 0.56-1.60; $P=.84$) for the all-cause mortality. Similarly, outcomes during the first 12 months of follow-up resulted in an adjusted HR of 1.08 (95% CI, 0.79-1.48, $P=.61$) for the primary outcome and 1.17 (95% CI,

Figure 2. Cumulative Event Rates Overall and for the US Cohort for Extended Follow-up

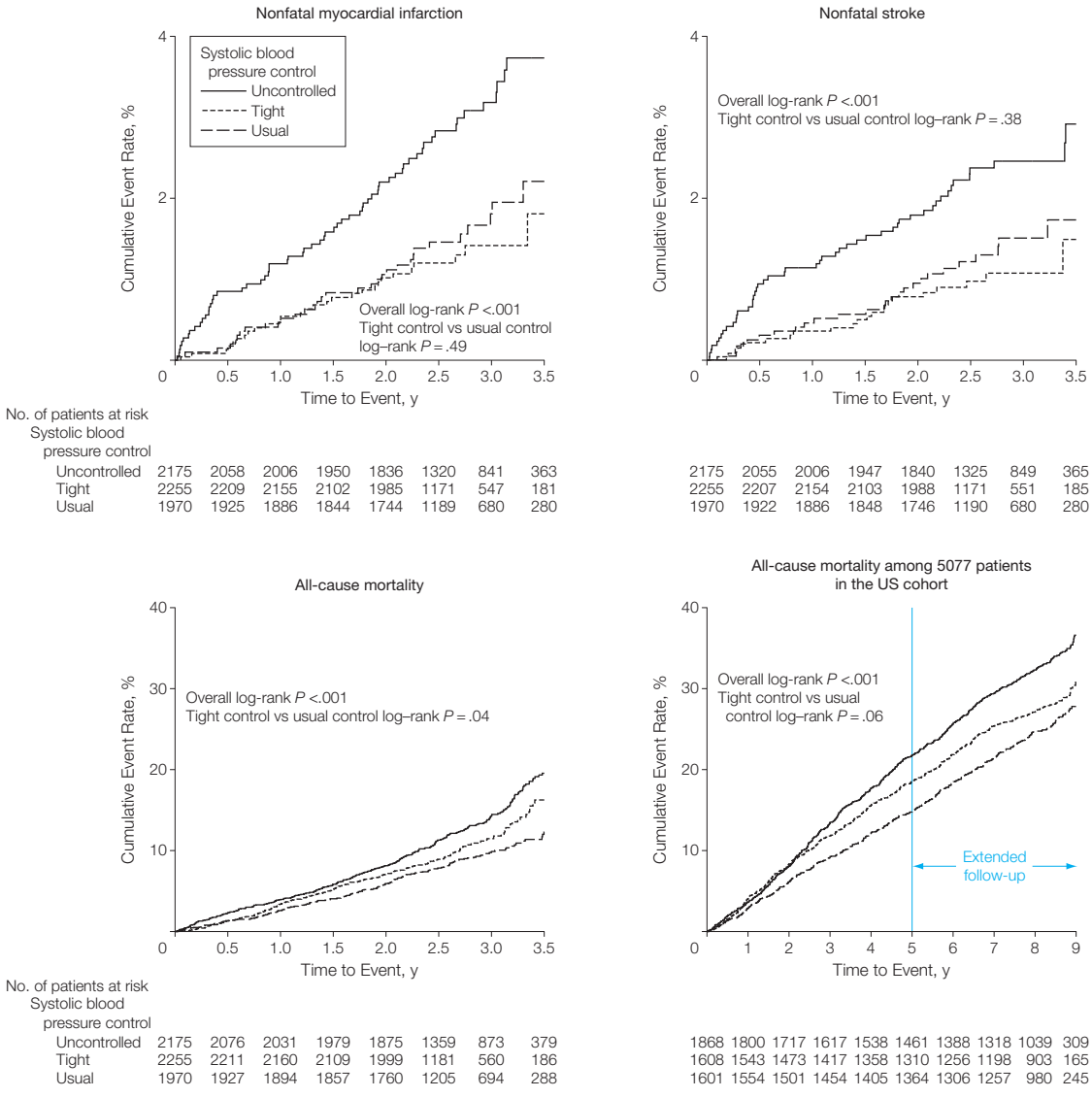
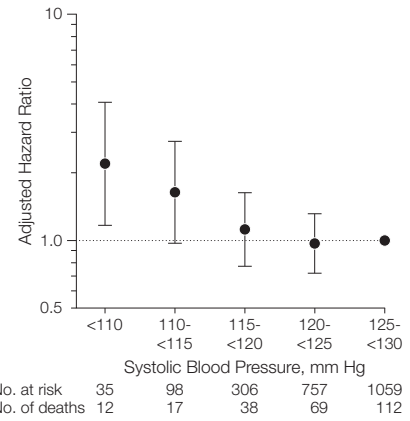


Figure 3. Adjusted Risk of All-Cause Mortality



The data points represent hazard ratios and the error bars, 95% confidence intervals for all-cause mortality in the diabetes cohort with average on-treatment systolic blood pressure of less than 130 mm Hg. The group represents those whose systolic blood pressure ranged from 125 to less than 130 mm Hg.

0.82-1.67; $P=.40$) for all-cause mortality.

Compared with a systolic BP range of 125 mm Hg to less than 130 mm Hg, those with a systolic BP range of 110 mm Hg to less than 115 mm Hg had an increased but not statistically significant risk (adjusted HR, 1.63; 95% CI, 0.97-2.75; $P=.06$) and systolic BP of less than 110 mm Hg was associated with significantly increased risk (adjusted HR, 2.18; 95% CI, 1.17-4.09; $P=.02$) of all-cause mortality (FIGURE 3).

COMMENT

The goal of treating hypertension in patients with diabetes is to prevent associated macrovascular and microvascular morbidity and mortality. Although for almost 20 years guidelines have recommended lower BP goals in patients with diabetes,[2] there is a paucity of evidence supporting this recommendation, particularly for lower systolic BP.[11,20] In this observational study, we have shown for the first time, to our knowledge, that decreasing systolic BP to lower than 130 mm Hg in patients with diabetes and CAD was not associated with further reduction in morbidity beyond that associated with systolic BP lower than 140 mm Hg, and, in fact, was associated with an increase in risk of all-cause mortality. Moreover, the increased mortality risk persisted over the long term.

The HOT study, which assigned participants to 3 different diastolic BP goals, showed that patients overall and those assigned to the subgroup of patients with diabetes who were assigned to the 80 mm Hg or less group had significantly reduced adverse outcomes compared with those assigned to higher diastolic BP groups.[3] However, although achieved BPs were not reported for the diabetes subgroup, overall, patients assigned to the 80 mm Hg or lower diastolic BP group actually achieved a mean (SD) BP of 139.7 (11.7)/81.1 (5.3) mm Hg, and only approximately 6% of the HOT population had CAD at entry.[3] The UKPDS, which enrolled only patients with diabetes, showed that patients assigned to the tight BP control group (<150/85 mm Hg) actually achieved a mean (SD) BP of 144 (14)/82 (7) mm Hg over 9 years of follow-up, which was associated with a significant reduction in microvascular and macrovascular events.[4] Although both of these landmark trials provided evidence to support benefits for the patients assigned to lower BP goals, it is important to note that on average, in neither trial was the goal met, and the systolic BP associated with the benefit observed in these trials was significantly higher than what is currently recommended (~140 vs <130 mm Hg) for patients with diabetes.[11] In fact, many of the major hypertension clinical trials published in the last decade have shown benefit with regard to cardiovascular and nephropathy risk reduction despite mean systolic BP higher than 130 mm Hg.[23]

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) study[24] randomized 4733 patients with hypertension to antihypertensive therapy that was considered either intensive (targeting a systolic BP of <120 mm Hg) or standard (targeting a systolic BP of <140 mm Hg) and evaluated risk for nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes over a mean follow-up of 4.7 years. Unlike HOT and UKPDS for which achieved BP exceeded the randomized target BP, ACCORD after a year of follow-up achieved a mean systolic BP in the intensive group of 119 mm Hg (95% CI, 118.9-119.7 mm Hg) and 133.5 mm Hg (95% CI, 133.1-133.8 mm Hg) in the standard group. This provided the first opportunity in a large randomized clinical trial to assess effects of achieving lower systolic BP in patients with diabetes. For the primary outcome, there was no difference comparing the intensive and standard therapy groups (HR, 0.88; 95% CI, 0.73-1.06; $P=.20$). Similarly, there was no difference comparing the groups with all-cause mortality and cardiovascular mortality. There was, however, reduction in risk of total stroke and nonfatal stroke observed in the intensive therapy group, although the overall annual stroke rate was very low (0.32% in the intensive group and 0.53% in the standard group). Importantly, the intensive therapy group had signficantly higher rates of serious adverse events attributed to antihypertensive therapy.[24]

The ACCORD results are somewhat surprising, particularly in light of the favorable results observed in UKPDS with regard to lower BP targets. However, in ACCORD, patients had lower systolic BP at baseline than was achieved in UKPDS,[4] suggesting the benefit observed in the tight-control group of UKPDS was likely based on reducing systolic BP from a mean 160 mm Hg at baseline to 144 mm Hg, and there is less benefit going from an average baseline systolic BP of 139 to 119 mm Hg as was observed in ACCORD.[24]

In the Appropriate Blood Pressure Control in Diabetes (ABCD) trial,[25] patients with diabetes were randomized to intensive vs moderate BP control groups. The mean BP achieved was 132/78 mm Hg in the intensive group and 138/86 mm Hg in the moderate BP control groups.[25] The ABCD investigators found that after 5 years, no difference existed between the intensive and moderate groups in the progression of diabetic retinopathy or neuropathy.

They also reported no difference in the rate of myocardial infarction, cerebrovascular events, or heart failure comparing the BP control groups. However, unlike in the present study, the ABCD participants in the intensive group had a significant reduction in all-cause mortality.[25] This may be explained by ABCD patients being on average a decade younger than those in our study and that only half had any history of cardiovascular disease; whereas all INVEST participants had documented CAD and thus were a higher-risk cohort and were more susceptible to the adverse effects of lower BP. The overall all-cause mortality rate in ABCD was 8% compared with 12.2% in the diabetes cohort of INVEST.

Results from the Irbesartan Diabetic Nephropathy Trial (IDNT) suggested that after a mean follow-up of 2.6 years, in patients with diabetic nephropathy, 60% of whom had a history of heart disease, achieving a systolic BP of 120 mm Hg or less was associated with an increase in all-cause mortality and cardiovascular mortality risk compared with those achieving systolic BP higher than 120 mm Hg.[26] The IDNT investigators concluded that BP of 120/85 mm Hg or less may be associated with an increase in cardiovascular events.[26] Although patients with creatinine levels of 4 mg/dL (to convert to μmol/L, multiply by 88.4) or more were excluded in INVEST, many had a diagnosis of renal impairment, and we observed a similar and significant increased mortality risk at systolic BP of less than 115 mm Hg.

The UKPDS performed an additional 10 years of follow-up that included in-person and questionnaire visits but no attempt to maintain previously assigned BP-lowering therapies. This long-term follow-up revealed a loss of the benefit realized in the tight-control group within the first 2 years after the study closed. When evaluating the 20-year period encompassing study and poststudy follow-up, there was no significant difference in the rate of any diabetes-related end point, myocardial infarction, microvascular disease, or all-cause mortality comparing the tight-control and less-tight control groups.[27] Our long-term follow-up data in the cohort of INVEST participants enrolled in the United States indicate that the increased risk of mortality observed in patients achieving tight control during study follow-up persisted in extended follow-up. Even though we have no BP data during extended follow-up, it is likely that patients were continued on the same or similar antihypertensive regimens and our data raise the possibility that continued maintanence of systolic BP lower than 130 mm Hg could be hazardous over the long term.

Our study has some limitations. This is a post hoc analysis and as such, represents observational data generated from a randomized, controlled clinical trial. We did not randomize a priori to the different systolic BP groups but rather categorized patients according to their achieved systolic BP within the context of the study. This could lead to possible sources of confounding. Individual patient characteristics over and above study treatment play a role in lowering BP. However, after adjustment for differences in baseline characteristics, there remained no difference in the risk of the primary outcome, nonfatal myocardial infarction, and nonfatal stroke comparing the tight-control with the usual-control group. Additionally, our data cannot be generalized to the population of patients with diabetes without CAD. However, as seen with ACCORD, conducting a randomized controlled trial to assess effects of lower systolic BP can also lead to possible sources of bias, including a priori sample selection with regard to level of BP and degree of cardiovascular risk at entry, which may play a role in the outcomes observed.

In conclusion, our data from this post hoc analysis in the cohort of patients with diabetes enrolled in INVEST indicate that tight control of systolic BP was not associated with improved cardiovascular outcomes compared with usual control. At this time, there is no compelling evidence to indicate that lowering systolic BP below 130 mm Hg is beneficial for patients with diabetes; thus, emphasis should be placed on maintaining systolic BP between 130 and 139 mm Hg while focusing on weight loss, healthful eating, and other manifestations of cardiovascular morbidity to further reduce long-term cardiovascular risk.

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REFERENCES

1. The 1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med*. 1984;144(5):1045-1057.
2. The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). *Arch Intern Med*. 1993;153(2):154-183.
3. Hansson L, Zanchetti A, Carruthers SG, et al; HOT Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet*. 1998;351(9118):1755-1762.
4. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 38. *BMJ*. 1998;317(7160):703-713.
5. Adler AI, Stratton IM, Neil HA, et al. Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): prospective observational study. *BMJ*. 2000;321(7258):412-419.
6. American Diabetes Association. Standards of medical care for patients with diabetes mellitus. *Diabetes Care*. 2002;25(1):213-229.
7. American Diabetes Association. Diabetic nephropathy. *Diabetes Care*. 2002;25:S85-S88.
8. American Diabetes Association. Standards of medical care in diabetes—2010. *Diabetes Care*. 2010;33(suppl 1):S11-S61.
9. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies Collaboration. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360(9349):1903-1913.
10. American Diabetes Association. Treatment of hypertension in adults with diabetes. *Diabetes Care*. 2002;25(1):199-201.
11. Chobanian AV, Bakris GL, Black HR, et al; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42(6):1206-1252.
12. Khosla N, Kalaitzidis R, Bakris GL. The kidney, hypertension, and remaining challenges. *Med Clin North Am*. 2009;93(3):697-715.
13. Rosendorff C, Black HR, Cannon CP, et al; American Heart Association Council for High Blood Pressure Research; American Heart Association Council on Clinical Cardiology; American Heart Association Council on Epidemiology and Prevention. Treatment of hypertension in the prevention and management of ischemic heart disease: a scientific statement from the American Heart Association Council for High Blood Pressure Research and the Councils on Clinical Cardiology and Epidemiology and Prevention. *Circulation*. 2007;115(21):2761-2788.
14. Verdecchia P, Staessen JA, Angeli F, et al; Cardio-Sis investigators. Usual versus tight control of systolic blood pressure in non-diabetic patients with hypertension (Cardio-Sis): an open-label randomised trial. *Lancet*. 2009;374(9689):525-533.
15. Bavry AA, Anderson RD, Gong Y, et al. Outcomes among hypertensive patients with concomitant peripheral and coronary artery disease: findings from the International Verapamil-SR/Trandolapril Study. *Hypertension*. 2010;55(1):48-53.
16. Messerli FH, Mancia G, Conti CR, et al. Dogma disputed: can aggressively lowering blood pressure in hypertensive patients with coronary artery disease be dangerous? *Ann Intern Med*. 2006;144(12):884-893.
17. Denardo SJ, Messerli FH, Gaxiola E, et al. Characteristics and outcomes of revascularized patients with hypertension: an international verapamil SR-trandolapril substudy. *Hypertension*. 2009;53(4):624-630.
18. Boutitie F, Gueyffier F, Pocock S, Fagard R, Boissel JP; INDANA Project Steering Committee. Individual Data Analysis of Antihypertensive Intervention. J-shaped relationship between blood pressure and mortality in hypertensive patients: new insights from a meta-analysis of individual-patient data. *Ann Intern Med*. 2002;136(6):438-448.
19. Bakris GL, Gaxiola E, Messerli FH, et al; INVEST Investigators. Clinical outcomes in the diabetes cohort of the International Verapamil SR-Trandolapril Study. *Hypertension*. 2004;44(5):637-642.
20. Mancia G, Laurent S, Agabiti-Rosei E, et al. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. *J Hypertens*. 2009;27:2121-2158.
21. Pepine CJ, Handberg-Thurmond E, Marks RG, et al. Rationale and design of the International Verapamil SR/Trandolapril Study (INVEST): an Internet-based randomized trial in coronary artery disease patients with hypertension. *J Am Coll Cardiol*. 1998;32(5):1228-1237.
22. Pepine CJ, Handberg EM, Cooper-DeHoff RM, et al; INVEST Investigators. A calcium antagonist vs a non-calcium antagonist hypertension treatment strategy for patients with coronary artery disease. The International Verapamil-Trandolapril Study (INVEST): a randomized controlled trial. *JAMA*. 2003;290(21):2805-2816.
23. Kalaitzidis R, Bakris GL. Lower blood pressure goals for cardiovascular and renal risk reduction: are they defensible? *J Clin Hypertens (Greenwich)*. 2009;11(7):345-347.
24. Cushman WC, Evans GW, Byington RP, et al; ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362(17):1575-1585.
25. Estacio RO, Jeffers BW, Gifford N, Schrier RW. Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. *Diabetes Care*. 2000;23(suppl 2):B54-B64.
26. Berl T, Hunsicker LG, Lewis JB, et al; Collaborative Study Group. Impact of achieved blood pressure on cardiovascular outcomes in the Irbesartan Diabetic Nephropathy Trial. *J Am Soc Nephrol*. 2005;16(7):2170-2179.
27. Holman RR, Paul SK, Bethel MA, Neil HA, Matthews DR. Long-term follow-up after tight control of blood pressure in type 2 diabetes. *N Engl J Med*. 2008;359(15):1565-1576.