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Safety and Efficacy of Low Blood Pressures Among Patients With Diabetes

Subgroup Analyses From the ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial)

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Objectives We sought to determine whether the blood pressure (BP) levels at which cardiovascular (CV) protection is achieved differ between diabetic and nondiabetic patients from the ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial).

Background Greater absolute benefits of BP reductions have been claimed for diabetic as compared with nondiabetic patients.

Methods A total of 25,584 patients (9,603 diabetic), older than 55 years, at high CV risk were randomized to ramipril, telmisartan, or both and observed for 4.6 years. We pooled the treatment arms to examine the relationships between BP and the primary composite outcome (CV death, nonfatal myocardial infarction or stroke, or hospitalized heart failure) and its components.

Results The primary outcome occurred in 1,938 (20.2%) diabetic patients and in 2,276 (14.2%) nondiabetic patients. Compared with nondiabetic patients, diabetic patients had a significantly higher risk for the primary endpoint (hazard ratio [HR]: 1.48; 95% confidence interval [CI]: 1.38 to 1.57) and CV death (HR: 1.56; 95% CI: 1.42 to 1.71); myocardial infarction (HR: 1.30 (95% CI: 1.17 to 1.46); stroke (HR: 1.39; 95% CI: 1.23 to 1.56); and congestive heart failure hospitalization (HR: 2.06; 95% CI: 1.82 to 2.32). The CV risk was significantly higher in diabetic than in nondiabetic patients regardless of the systolic BP changes during treatment. In both diabetic and nondiabetic patients, progressively greater systolic BP reductions were accompanied by reduced risk for the primary outcome only if baseline systolic BP levels ranged from 143 to 155 mm Hg; except for stroke, there was no benefit in fatal or nonfatal CV outcomes by reducing systolic BP below 130 mm Hg.

Conclusions The relationship between BP and overall CV risk had a similar pattern in diabetic and nondiabetic patients over a wide range of baseline and in-treatment BP values although, for the same systolic BP, a higher risk is observed in diabetic patients. (Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial [ONTARGET]; NCT00153101) (J Am Coll Cardiol 2012;59:74–83) © 2012 by the American College of Cardiology Foundation

Observational studies have shown that the cardiovascular (CV) sequelae of diabetes increase progressively with increased blood pressure (BP) across a large range of BP values (1–4). Furthermore, randomized clinical trials have documented that in diabetes, BP reductions by drug treatment are associated with a reduction of diabetes-related

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macrovascular and microvascular complications (5–8). Finally, greater absolute benefits of BP reductions have been claimed for diabetic as compared with nondiabetic patients, although a meta-analysis concluded that there was limited evidence that lower BP goals produced larger reductions in total major CV events in individuals with diabetes compared with those without (9).

Guidelines have recommended more aggressive antihypertensive treatment in diabetes, aiming at values <130 mm Hg systolic and 80 mm Hg diastolic. However, the additional beneficial effects of such lower BP targets remain unproven (8–12). The recent results of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) (13), showed that in patients with type 2 diabetes, targeting systolic BP to <120 mm Hg did not reduce the rate of CV events, compared with subjects in whom the systolic BP target was <140 mm Hg, except for stroke. Likewise, a post hoc analysis of the INVEST (International Verapamil SR-Trandolapril Study) concluded that reducing systolic BP to <130 mm Hg in patients with diabetes and coronary artery disease was not associated with improved CV outcomes compared with usual BP control (14).

The recently published ONTARGET (ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) (15) provides an opportunity to determine in a large number of patients whether the BP at which CV protection is achieved differs between diabetic and nondiabetic patients during treatments based on blockade of the renin-angiotensin system. We have analyzed the data to examine this question. In addition, we have explored whether BP reduction in high-risk diabetic patients impacts outcomes differently than in nondiabetic patients.

Methods

Between January 2002 and June 2003, 25,584 patients older than 55 years, of whom 9,603 had diabetes, were randomized to ramipril, telmisartan, or both in a multicenter double-blind trial performed in 40 countries. The eligibility criteria and details of the protocol have been reported previously (16,17). Briefly, patients had to have 1 or more previous CV events or diabetes with end-organ damage. After written informed consent, patients entered a single-blind run-in period in which they received ramipril and telmisartan in progressive doses for 3 to 4 weeks. Patients who tolerated the run-in period were then randomized to receive 80 mg of telmisartan once daily, 5 mg of ramipril once daily, or their combination for 2 weeks. The dose of ramipril was increased to 10 mg in the 2 relevant arms.

Abbreviations and Acronyms

BP = blood pressure
CI = confidence interval
CV = cardiovascular
HR = hazard ratio

Except for angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, the addition of other antihypertensive drugs was allowed to achieve the target BP values recommended by guidelines in high-risk patients. Follow-up visits occurred at 6 weeks, 6 months, and then every 6 months until the last scheduled visit. At each visit, BP was measured in duplicate after a 3-min rest with the patient in the sitting position using a semiautomatic validated (18) device (Model HEM-757, OMRON Healthcare, Vernon Hills, Illinois). BP values from baseline to the time of the event or to the final protocol visit were used for the analysis.

The primary outcome of the study was a composite of CV death, myocardial infarction, stroke, or hospitalization for congestive heart failure as adjudicated by a central committee. Secondary outcomes were the primary outcome components. Since in the Cox regression model the relation between outcome and treatment allocation showed no significant differences, and treatment uniformly consisted of drugs blocking the renin-angiotensin system, data for the 3 treatment groups were pooled to allow the analysis to be made on a large number of patients.

Statistical analysis. Analyses were conducted with SAS 8.2 release (SAS Institute, Cary, North Carolina) using the Cox regression model. Since the trial included patients above 55 years of age, data analysis was focused on systolic BP, which in the elderly is more predictive than diastolic BP (19).

The relation between baseline systolic BP, divided into quartiles (first: 95 to 130 mm Hg, second: 131 to 142 mm Hg, third: 143 to 154 mm Hg, and fourth: 155 to 200 mm Hg), and risk of the primary and other outcomes was explored using Cox regression, as well as the relation between outcome and the magnitude of systolic BP changes during follow-up, divided into tertiles, for each systolic BP entry quartile. We tested for a quadratic relationship of outcome with in-treatment systolic BP, because the relationship was nonlinear. The nadir was derived from the resulting quadratic function, and confidence intervals (CIs) were calculated using the delta method (20). The risk of primary as well as of other outcomes in patients with or without diabetes at baseline was calculated before and after adjustment for age, gender, and the following baseline covariates: current smoking, ethnicity, body mass index, serum creatinine, history of CV disease, and use of aspirin, statins, diuretics, or beta-blockers. We did not adjust the association of systolic BP and outcomes for pulse pressure because of the strong colinearity between the 2 measures. Hazard ratios (HRs) and 95% CIs were calculated in estimat-

on the Speaker's Bureau for Boehringer-Ingelheim, Daiichi Sankyo, Forest Pharmaceuticals, and Novartis; and serves as a consultant for Boehringer-Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Forest Pharmaceuticals, Novartis, and Takeda Pharmaceuticals. Dr. Bohm has received study and speaker fees from Boehringer-Ingelheim. Dr. Williams has received a research grant from Boehringer-Ingelheim as an investigator in the ONTARGET study. Dr. Yusuf has received research grants and honoraria for speaking and consulting from Sanofi, Boehringer-Ingelheim, Bristol-Myers Squibb, Novartis, and Servier. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Part of these data were presented at the Milan meeting of the European Society of Hypertension, Milan, Italy, June 2008.

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ing the levels of risk. Finally, characteristics of patients who suffered from a myocardial infarction or died because of CV disease were compared with those who did not experience an event by using analysis of variance. In these 2-tailed tests, p values <0.05 were considered significant. No corrections were made for multiple testing.

Results

Baseline characteristics of the study population and description of outcomes. The general characteristics of the study population, including treatments other than the trial medication, are shown in Table 1, separately for diabetic and nondiabetic patients. During the 4.5 years of follow-up (median: 4.6 years), the primary outcome occurred in 1,938 (20.2%) diabetic patients and in 2,276 (14.2%) nondiabetic patients. There was also a relatively large number of cause-specific CV events that were more common in diabetic than in nondiabetic patients. The respective figures were 506 (5.3%) and 622 (3.9%) for strokes, 544 (5.7%) and 710 (4.4%) for nonfatal myocardial infarctions, 868 (9.0%) and 948 (5.9%) for CV deaths, and 587 (6.1%) and 492 (3.1%) hospital admissions for heart failure. Compared with nondiabetic patients, diabetic patients had a significantly higher risk for the main outcome (HR: 1.48, 95% CI: 1.38 to 1.57) and cause-specific events: CV death (HR: 1.56; 95% CI: 1.42 to 1.71); myocardial infarction (HR: 1.30; 95% CI: 1.17 to 1.46); stroke (HR: 1.39; 95% CI: 1.23 to 1.56); congestive heart failure hospitalization (HR: 2.06; 95% CI: 1.82 to 2.32).

Baseline systolic BP and outcomes. Figure 1 shows the unadjusted Kaplan-Meier plots for outcomes in relation to quartiles of systolic BP value. For the same baseline systolic BP, diabetic patients consistently had a higher risk of the primary outcome and of all its components than nondiabetic patients. There was a statistically significant association between baseline systolic BP and the incidence of stroke in both diabetic and nondiabetic patients ($p < 0.01$, comparing stroke incidence in the first with the third or fourth quartiles). Stroke was primarily responsible for the progressively higher incidence of the primary outcome with higher baseline systolic BP because there was no relationship between baseline systolic BP and the incidence of other events, that is, CV death, myocardial infarction, or hospitalized heart failure.

Table 2 shows the HRs for the primary outcome and its components in relation to baseline systolic BP, taking the lowest systolic BP quartile of nondiabetic patients as the reference. Diabetic subjects had higher risk than nondiabetic patients whichever systolic BP quartile was considered. In both diabetic patients and nondiabetic patients, there were significant differences between the first and the third and fourth quartiles for stroke. In contrast, no between-quartile differences were seen for the primary outcome, CV mortality, myocardial infarction, and hospitalized heart failure. Compared with the first quartile, the second quartile showed a lower risk of myocardial infarction and heart failure, but this disappeared with data adjustment.

Table 1 General Characteristics of the Study Population

	Nondiabetic Patients (n = 15,981)	Diabetic Patients (n = 9,603)
Demographics		
Female	3,663 (22.9)	3,154 (32.8)
Age, yrs	66.6 ± 7.4	66.1 ± 6.7
Ethnicity		
European/Caucasian	12,376 (77.1)	6,432 (67.0)
Asians	2,001 (12.5)	1,519 (15.8)
Black African	268 (1.7)	301 (3.1)
Other	1,334 (5.3)	1,351 (14.1)
Medical history		
Hypertension	9,991 (62.5)	7,601 (79.2)
Current smoking	2,149 (13.4)	1,075 (11.2)
CAD	13,144 (82.3)	5,929 (61.7)
MI	8,886 (55.6)	3,644 (38.0)
Angina	7,819 (48.9)	3,668 (38.2)
PAD	2,040 (12.8)	1,424 (14.8)
Stroke/TIA	3,360 (21.0)	1,566 (16.4)
Medication		
Beta-blockers	9,743 (60.9)	4,831 (50.3)
Calcium channel blockers	4,911 (30.7)	3,554 (37.0)
Diuretics	3,686 (23.0)	3,472 (36.2)
Statins	10,519 (65.7)	5,253 (54.7)
ASA	12,799 (80.0)	6,590 (68.6)
ACE inhibitors	8,468 (52.9)	6,272 (65.3)
ARB	1,154 (7.2)	1,054 (11.0)
Insulin	0 (0)	2,653 (27.6)
Oral glucose-lowering agents	0 (0)	6,425 (66.9)
Physical, mean		
SBP, mm Hg	140.7 ± 17.6	143.7 ± 16.91
DBP, mm Hg	82.2 ± 10.5	81.8 ± 10.28
Pulse pressure, mm Hg	81.8 ± 11.0	61.9 ± 13.84
Body mass index	27.5 ± 29.3	29.2 ± 4.91
Laboratory, mean		
Serum creatinine, mmol/l	96.8 ± 26,4	95.0 ± 27.6
Glucose, mmol/l	5.5 ± 1.0	8.6 ± 3.2
Cholesterol, mmol/l	4.9 ± 1.1	5.0 ± 1.2
HDL, mg/dl	1.3 ± 0.4	1.2 ± 0.4
LDL, mg/dl	2.9 ± 1.0	2.9 ± 1.0
Triglycerides mmol/l	1.7 ± 1.0	1.9 ± 1.3

Values are n (%) or mean ± SD.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ASA = aspirin; CAD = coronary artery disease; DBP = diastolic blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MI = myocardial infarction; PAD = peripheral artery disease; SBP = systolic blood pressure; TIA = transitory ischemic attack.

Systolic BP changes during treatment and outcomes. In-treatment BP values were the mean of all the values before the event or until the final visit, excluding baseline values. As shown in Figure 2, treatment reduced systolic BP in each baseline systolic BP quartile, the average in-treatment quartile values being 125.8 ± 12.0 mm Hg, 132.4 ± 11.2 mm Hg, 137.7 ± 11.5 mm Hg, and 144.3 ± 12.6 mm Hg. The CV risk was significantly higher in diabetic patients than in

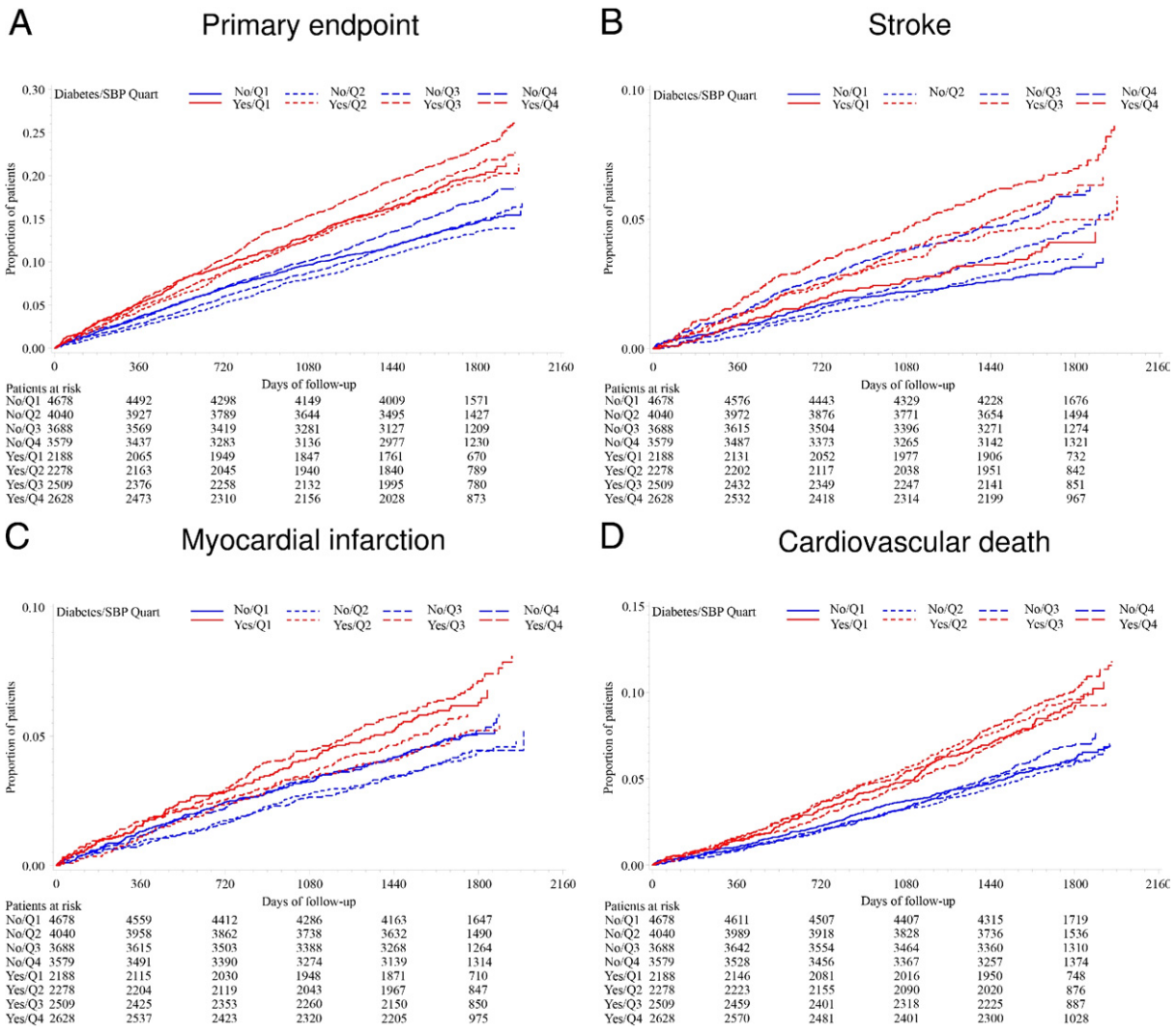

Figure 1 **Kaplan-Meier Curves Relating Baseline SBP**

Systolic blood pressure (SBP) measurements were divided into quartiles (first: 95 to 130 mm Hg, second: 131 to 142 mm Hg, third: 143 to 154 mm Hg, fourth: 155 to 200 mm Hg), to the cumulative hazard of the primary outcome **(A)**, stroke **(B)**, myocardial infarction **(C)**, and cardiovascular mortality **(D)**, in both diabetic patients and nondiabetic patients.

nondiabetic patients regardless of the systolic BP change during treatment. In both diabetic patients and nondiabetic patients, the progressively greater systolic BP reduction from the first to the third tertile was accompanied by a reduction in the risk for the primary outcome only if baseline systolic BP ranged from 143 to 155 mm Hg. With 1 exception, this was the case also for stroke, the progressively greater systolic BP reduction from the first to the third tertile was usually associated with no reduction in either CV mortality or myocardial infarction. In any case, no significant interaction was observed for BP and diabetes in the outcomes risk. The results were similar when data were adjusted for covariates (data not shown). In the adjusted data, there was no evidence of any adverse effect of low systolic BP on any CV outcome, except for CV mortality, which in patients with a baseline systolic BP <130 mm Hg showed a significant increase in the tertile with the greatest systolic BP reduction. In this low baseline systolic BP quartile, the risk of CV mortality increased progressively from the tertile with a small systolic BP increase to that with a larger systolic BP reduction ($p < 0.01$ for trend). Consequently, the beneficial impact of BP reduction was similar in both groups of subjects although the risk reduction was greater in diabetic patients as compared with nondiabetic patients as a result of the highest baseline risk.

The incidence of CV events for deciles of in-treatment systolic BP is shown in Figure 3. There was a progressive reduction in the incidence of stroke down to 115 mm Hg systolic BP. In contrast, a "J-curve" relationship was observed for the other outcomes. For the primary outcome, the

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Table 2 Risk of Primary Study Outcome and Other Outcome Events According to SBP at Entry (First Visit)

Model	Hazard Ratio (95% Confidence Interval)				
	Primary Composite Outcome	Cardiovascular Death	Myocardial Infarction	Hospitalization Due to CHF	Stroke
Unadjusted					
Quartile 1					
No DM	1.00	1.00	1.00	1.00	1.00
DM	1.46 (1.37–1.55)	1.55 (1.41–1.70)	1.30 (1.16–1.45)	2.06 (1.83–2.32)	1.33 (1.18–1.50)
Quartile 2					
No DM	0.93 (0.85–1.02)	0.97 (0.85–1.11)	0.82 (0.70–0.96)*	0.83 (0.70–0.98)*	1.17 (0.97–1.40)
DM	1.36 (1.22–1.51)	1.51 (1.29–1.76)	1.07 (0.88–1.30)	1.71 (1.39–2.10)	1.55 (1.25–1.93)
Quartile 3					
No DM	1.03 (0.94–1.12)	0.97 (0.85–1.11)	0.87 (0.74–1.02)	0.89 (0.75–1.05)	1.47 (1.23–1.75)*
DM	1.50 (1.35–1.66)	1.50 (1.29–1.76)	1.13 (0.94–1.36)	1.84 (1.51–2.24)	1.95 (1.59–2.40)†
Quartile 4					
NO DM	1.18 (1.09–1.28)*	1.11 (0.98–1.26)	1.07 (0.92–1.24)	0.94 (0.80–1.10)	1.83 (1.54–2.16)*
DM	1.72 (1.56–1.90)†	1.71 (1.47–1.99)	1.39 (1.16–1.66)	1.93 (1.59–2.35)	2.43 (2.00–2.96)†
Adjusted by age and sex					
Quartile 1					
No DM	1.00	1.00	1.00	1.00	1.00
DM	1.54 (1.45–1.64)	1.65 (1.50–1.81)	1.37 (1.22–1.53)	2.16 (1.92–2.44)	1.38 (1.23–1.56)
Quartile 2					
No DM	0.91 (0.83–0.99)†	0.94 (0.82–1.07)	0.81 (0.69–0.95)*	0.80 (0.67–0.95)*	1.14 (0.95–1.36)
DM	1.39 (1.25–1.55)	1.55 (1.32–1.81)	1.11 (0.92–1.34)	1.73 (1.40–2.12)†	1.57 (1.27–1.95)
Quartile 3					
No DM	0.97 (0.89–1.06)	0.90 (0.79–1.02)	0.85 (0.72–0.99)*	0.82 (0.69–0.97)*	1.39 (1.17–1.66)*
DM	1.49 (1.35–1.66)	1.48 (1.26–1.73)	1.16 (0.96–1.39)	1.77 (1.45–2.16)†	1.92 (1.57–2.36)†
Quartile 4					
No DM	1.07 (0.98–1.16)	0.96 (0.84–1.09)	1.02 (0.87–1.18)	0.81 (0.68–0.95)*	1.66 (1.40–1.96)*
DM	1.64 (1.49–1.81)	1.58 (1.36–1.84)	1.39 (1.16–1.66)	1.74 (1.43–2.12)†	2.30 (1.88–2.80)†
Full adjustment‡					
Quartile 1					
No DM	1.00	1.00	1.00	1.00	1.00
DM	1.35 (1.25–1.46)	1.38 (1.22–1.55)	1.39 (1.20–1.60)	1.64 (1.41–1.91)	1.33 (1.14–1.54)
Quartile 2					
No DM	0.92 (0.84–1.01)	0.97 (0.85–1.11)	0.86 (0.73–1.01)	0.88 (0.74–1.04)	1.10 (0.91–1.33)
DM	1.25 (1.11–1.41)	1.34 (1.12–1.60)	1.19 (0.96–1.48)	1.44 (1.15–1.81)	1.46 (1.15–1.85)
Quartile 3					
No DM	0.97 (0.89–1.06)	0.89 (0.78–1.03)	0.88 (0.75–1.04)	0.89 (0.75–1.06)	1.29 (1.08–1.55)*
DM	1.31 (1.17–1.47)	1.23 (1.03–1.47)	1.23 (0.99–1.52)	1.46 (1.17–1.83)	1.72 (1.36–2.16)†
Quartile 4					
No DM	1.05 (0.96–1.15)	0.96 (0.84–1.10)	1.06 (0.91–1.24)	0.86 (0.73–1.02)	1.47 (1.24–1.75)*
DM	1.42 (1.27–1.60)	1.32 (1.11–1.57)	1.47 (1.19–1.81)	1.42 (1.13–1.77)	1.95 (1.56–2.44)†

Quartiles of baseline systolic blood pressure (in mm Hg): ≤130, >130 to ≤142, >142 to ≤154, >154. *$p < 0.05$ referred to quartile 1 within nondiabetic patient group; †$p < 0.05$ referred to quartile 1 within diabetic patient group; ‡adjusted by the following covariates (all included in the model): age (years), gender, smoking (current, formerly, never), ethnicity (Caucasian, Asian, Black, other), body mass index (kg/m^2), serum creatinine (mg/l), plasma glucose (mg/dl), low-density lipoprotein cholesterol (mg/dl), history of cardiovascular diseases (previous myocardial infarction, previous stroke, angina [yes or no]), use of aspirin, statins, diuretics, or β-blockers (yes or no).

CHF = congestive heart failure; DM = diabetes mellitus; SBP = systolic blood pressure.

nadir of the J-curve lay at about 129.6 mm Hg (122.1 to 137.0 mm Hg) systolic BP for diabetic patients and 129.0 mm Hg (123.9 to 134.1 mm Hg) for nondiabetic patients. For CV death, it lies at 135.6 mm Hg (130.6 to 140.5 mm Hg) and 133.1 mm Hg (128.8 to 137.4 mm Hg), respectively, in diabetic patients and nondiabetic patients. No nadir was observed for myocardial infarction or stroke. Achieving systolic BP of 130 mm Hg instead of 140 mm Hg reduced the risk for the primary outcome by 3.4% in diabetic patients and 4% in nondiabetic patients; for CV death, 0% and 1.9%; for myocardial infarction −3.7% and 0.1%; and for stroke 31.4% and 21.7%, respectively.

Influence of in-trial diastolic BP. The association between in-trial diastolic BP and outcomes at any level of achieved systolic BP is shown in Figure 4. For the primary outcome, both diabetic and nondiabetic patients showed that the highest risk occurred in subjects with the lowest or highest in-trial diastolic BP (67.2 and 86.7 mm Hg, respectively), whatever the systolic BP values. The increase in risk in the lowest diastolic BP quartile was even greater in

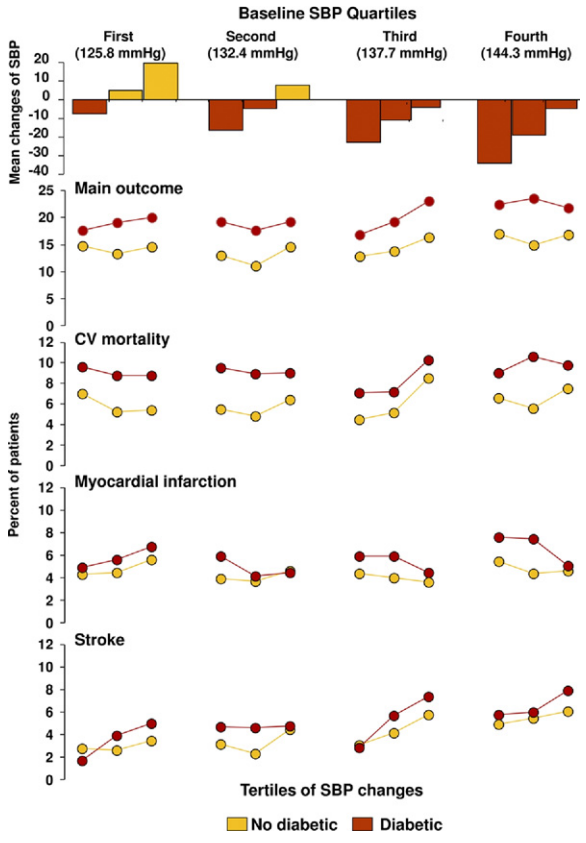

Figure 2 **Tertile Changes in SBP Induced by Treatment and Cardiovascular Outcomes**

Changes within each quartile of baseline systolic blood pressure (SBP) in diabetic patients and nondiabetic patients are shown. CV = cardiovascular.

diabetic patients than in nondiabetic patients. A similar trend was observed for CV mortality, whereas myocardial infarction showed no distinct pattern. Compared with the remaining 3 quartiles, the risk for stroke was maximal in the quartile with the highest diastolic BP value.

Characteristics of the group with a low systolic BP at baseline. In patients with a systolic BP <130 mm Hg at baseline, the characteristics of patients who suffered from a myocardial infarction or died for CV disease were compared with those who did not experience an event (Table 3). In both the diabetic and nondiabetic groups, patients who suffered an event had an older age, a previous history of coronary or peripheral artery disease, a lower ankle–arm BP ratio, a higher heart rate, a higher serum creatinine value, and a greater use of diuretics. Diabetic patients who suffered from an event also had more insulin treatment and more frequent smoking. In contrast, no differences in baseline and mean BP changes during treatment were observed. In a Cox hazard risk analysis of the subjects with initial systolic BP <130 mm Hg, after adjusting for the baseline variables, the risk to have events was increased in diabetes (HR: 1.29, 95% CI: 1.05 to 1.58), older age (HR: 1.04, 95% CI: 1.03 to 1.05), current smokers (HR: 1.52, 95%CI: 1.19 to 1.95), high creatinine levels (HR: 2.23, 95% CI: 1.72 to 2.90), previous myocardial infarction (HR 1.72, 95% CI: 1.43 to 2.07), previous angina (HR: 1.48, 95% CI: 1.25 to 1.75), and use of diuretics (HR: 1.56, 95% CI: 1.31 to 1.86). In contrast, treatment with statins (HR: 0.76, 95% CI: 0.63 to 0.91) was associated with lower risk. Concerning BP values, increment in systolic BP was associated with lower risk (HR: 0.98, 95% CI: 0.97 to 0.99), whereas increment in diastolic BP was associated with higher risk (HR: 1.02, 95% CI: 1.00 to 1.03). An increment in systolic BP of 10 mm Hg was associated with risk reduction by 13% and an increment in DBP with increment of risk by 18%.

Discussion

Our post-hoc analysis of the large ONTARGET database shows that in patients with a history of CV disease or diabetes with end-organ damage, the incidence of CV morbidity and fatal events was markedly higher (adjusted risk about +50%, +30%, and +40% for CV mortality, myocardial infarction, and stroke, respectively) in the presence of diabetes at each level of baseline or achieved BP. This confirms the results of previous studies (21,22) that diabetes sharply increases CV risk and that this occurs regardless of the BP level. It also shows that diabetes continues to magnify CV risk, even in patients at high CV risk for other reasons.

The principal finding of the present study is that the relationship between BP and overall CV risk had a similar pattern in diabetic and nondiabetic patients over a wide range of baseline and in-treatment BP values. The role of diabetes was to shift the relationship of events with BP upward compared with that in the nondiabetic group. So, we can suggest that as far as the relationship with BP is concerned there may be no reason to consider diabetics separately from other high-risk patients. This applies also to the effect of BP-lowering treatment. In this respect, our findings do not support the claim that the relationship between BP reductions and CV risk reduction is steeper in diabetes (9), and it is agreement with a recent published study (23).

In the diabetic patients, the risk of stroke showed a clear-cut relationship with systolic BP throughout a wide range of initial and in-treatment values. The adjusted risk of stroke continued to decrease down to achieved systolic BP values of 115 mm Hg, with no evidence of an upward J-curve inflection. This is consistent with the conclusions drawn from retrospective analyses of trials on patients with a history of stroke (24) or coronary heart disease (25,26), which indicate that as far as protection against stroke is concerned, the lower the achieved BP, the better.

The relationship of initial or in-treatment systolic BP with myocardial infarction or CV mortality was different from that for stroke because the risk of either event was not significantly related to the baseline systolic BP value and was

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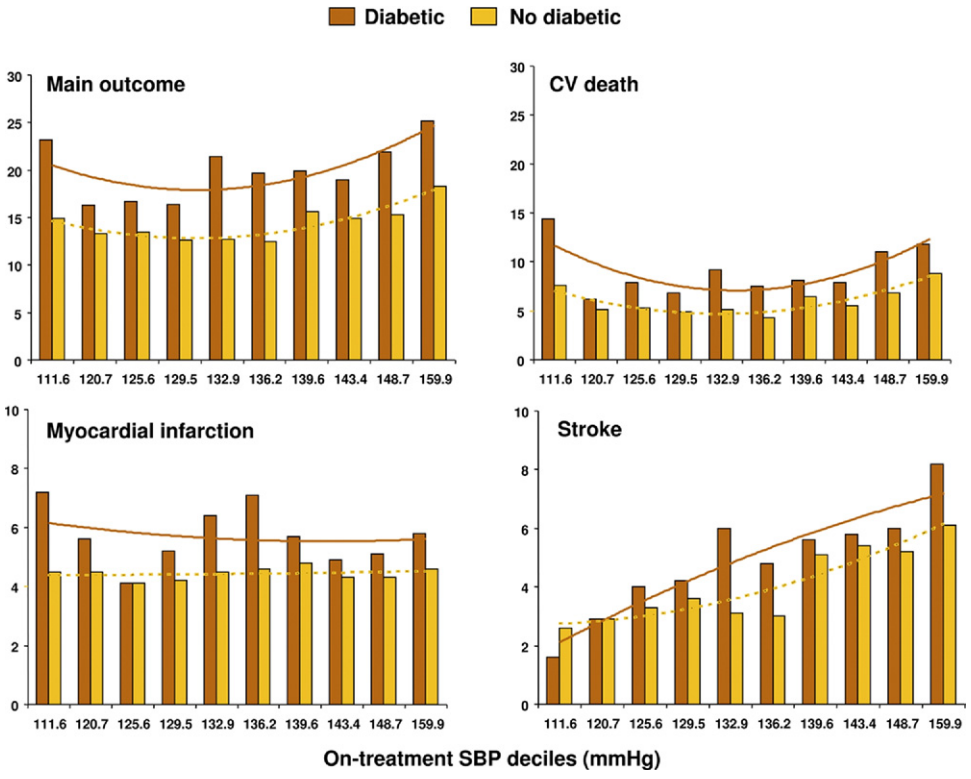

Figure 3 Proportion of Outcome Events by Achieved SBP, Divided Into Deciles

The quadratic relationship between in-treatment systolic blood pressure (SBP) and events is shown separately for diabetic patients and nondiabetic patients. CV = cardiovascular.

flat over a wide range of in-treatment values, i.e. between 155 and 115 mm Hg. It should be emphasized that the differing relationship of systolic BP to stroke and to cardiac events was the reason for the limited relationship of baseline and in-treatment systolic BP with the primary composite outcome, which included both types of events.

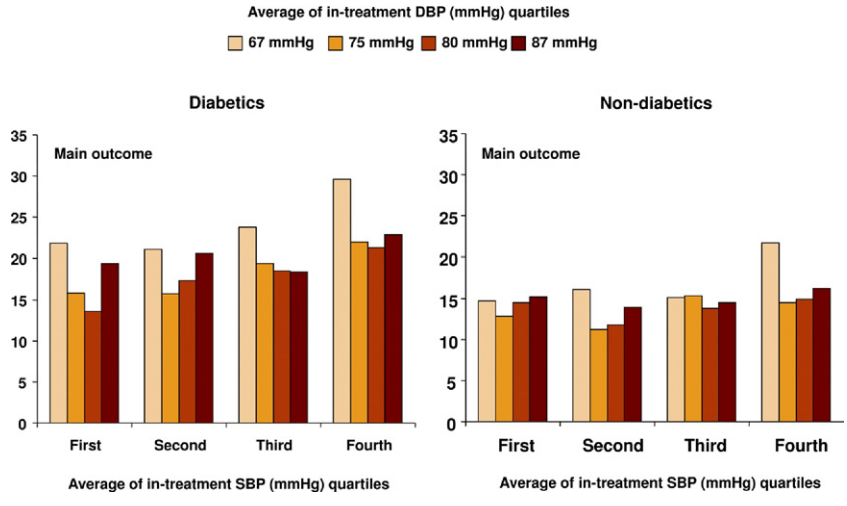

Figure 4 Primary Outcome in Relation to Achieved DBP

Results are divided into quartiles and are for any level of achieved systolic blood pressure (SBP) in both diabetic patients and nondiabetic patients. DBP = diastolic blood pressure.

Table 3 Characteristics of the Patients Who Had MI or CV Death Compared With Those That Did Not Have Events in the Baseline Low BP Group (SBP <130 mm Hg)

	Nondiabetic Patients			Diabetic Patients		
	No Events	Events	p Value	No Events	Events	p Value
n	3,722 (90.1)	410 (9.9)		1,597 (86.3)	253 (13.7)	
Demographics						
Female	777 (20.9)	65 (15.9)	0.0166	438 (27.4)	68 (26.9)	0.8556
Age	65.0 ± 7.0	67.2 ± 7.9	<0.0001	64.7 ± 6.8	67.4 ± 7.4	<0.0001
Age ≥65 yrs	1,781 ± 47.9	239 ± 58.3	<0.0001	771 ± 48.3	158 ± 62.5	<0.0001
Ethnicity			0.1990			0.1049
European/Caucasian	2,868 (77.1)	316 (77.1)		1034 (64.7)	182 (71.9)	
Asians	482 (13.0)	42 (10.2)		316 (19.8)	35 (13.8)	
Black African	48 (1.3)	8 (2.0)		55 (3.4)	9 (3.6)	
Other	324 (8.7)	43 (10.5)		192 (12.0)	27 (10.7)	
Medical history						
Hypertension	1,721 (46.2)	202 (49.3)	0.2431	1,058 (66.2)	170 (67.2)	0.7676
Current smoking	540 (14.5)	83 (20.3)	0.0019	236 (14.8)	33 (13.0)	0.4627
Angina	1,892 (50.8)	227 (55.4)	0.0814	646 (40.5)	137 (54.2)	<0.0001
CAD	3,272 (87.9)	375 (91.5)	0.0339	1,083 (67.8)	211 (83.4)	<0.0001
MI	2,375 (63.8)	301 (73.4)	0.0001	722 (45.2)	148 (58.5)	<0.0001
PAD	354 (9.5)	63 (15.4)	0.0002	175 (11.0)	51 (20.2)	<0.0001
Stroke/TIA	622 (16.7)	78 (19.0)	0.2360	256 (16.0)	49 (19.4)	0.1838
CABG or PTCA	2047 (55.0)	208 (50.7)	0.0997	683 (42.8)	117 (46.3)	0.2996
Medication						
Beta-blockers	2,468 (66.3)	263 (64.1)	0.3801	875 (54.8)	151 (59.7)	0.1456
Calcium channel blockers	958 (25.7)	103 (25.1)	0.7861	478 (29.9)	76 (30.0)	0.9721
Diuretics	746 (20.0)	122 (29.8)	<0.0001	547 (34.3)	139 (54.9)	<0.0001
Statins	2,692 (72.3)	268 (65.4)	0.0030	966 (60.5)	147 (58.1)	0.4714
ASA	3,076 (82.6)	325 (79.3)	0.0891	1,168 (73.1)	198 (78.3)	0.0849
ACE inhibitors	2,013 (54.1)	254 (62.0)	0.0025	1,007 (63.1)	193 (76.3)	<0.0001
ARB	236 (6.3)	22 (5.4)	0.4433	157 (9.8)	18 (7.1)	0.1755
Insulin	—	—	—	410 (25.7)	89 (35.2)	0.0016
Oral glucose-lowering agents	—	—	—	1,069 (66.9)	157 (62.1)	0.1270
Physical, mean						
Heart rate, beats/min	65.4 ± 12.0	68.3 ± 12.4	<0.0001	70.7 ± 12.1	73.0 ± 14.8	0.0211
SBP, mm Hg	118.7 ± 8.1	118.1 ± 8.7	0.1708	119.6 ± 7.9	118.7 ± 8.6	0.1524
DBP, mm Hg	73.8 ± 8.4	72.4 ± 9.1	0.0021	72.9 ± 8.6	71.9 ± 9.3	0.0892
Pulse pressure, mm Hg	44.9 ± 8.5	45.7 ± 9.4	0.0856	46.6 ± 8.9	46.9 ± 9.5	0.7054
SBP change,* mm Hg	5.1 ± 12.3	4.4 ± 14.4	0.3552	8.7 ± 12.7	9.1 ± 15.2	0.6964
DBP change,* mm Hg	−0.3 ± 8.7	0.2 ± 10.2	0.3359	1.2 ± 8.8	2.1 ± 10.4	0.2369
Arm/leg BP ratio, right	0.92 ± 0.28	0.96 ± 0.18	0.0003	0.93 ± 0.18	0.98 ± 0.20	0.0004
Arm/leg BP ratio, left	0.92 ± 0.33	0.95 ± 0.20	0.0019	0.93 ± 0.18	0.99 ± 0.30	0.0025
Body mass index, kg/m^2	27.2 ± 4.2	27.1 ± 4.5	0.4788	29.1 ± 5.4	29.4 ± 6.1	0.4363
Waist circumference, cm	94.2 ± 12.7	94.7 ± 12.8	0.4666	97.9 ± 14.1	100.0 ± 15.3	0.0367
Waist/hip ratio	0.94 ± 0.08	0.95 ± 0.08	0.0104	0.95 ± 0.08	0.96 ± 0.08	0.0521
Laboratory, mean						
Serum creatinine, mg/dl	92.4 ± 21.1	98.6 ± 26.4	<0.0001	93.3 ± 25.5	110.0 ± 35.2	<0.0001
Glucose, mg/dl	5.4 ± 0.9	5.5 ± 1.1	0.1333	8.2 ± 3.1	8.7 ± 3.3	0.0435
Cholesterol, mg/dl	4.7 ± 1.0	4.8 ± 1.0	0.3348	4.8 ± 1.1	4.8 ± 1.3	0.4346
HDL, mg/dl	1.2 ± 0.4	1.2 ± 0.4	0.0520	1.2 ± 0.4	1.1 ± 0.4	0.0133
LDL, mg/dl	2.8 ± 0.9	2.9 ± 0.9	0.1546	2.7 ± 0.9	2.8 ± 1.0	0.7345
Triglycerides, mg/dl	1.6 ± 1.0	1.6 ± 0.9	0.7485	1.9 ± 1.4	2.2 ± 1.6	0.0400

Values are n (%) or mean ± SD.

BP = blood pressure; CABG = coronary artery bypass graft surgery; CV = cardiovascular; PTCA = percutaneous transluminal coronary angioplasty; other abbreviations as in Table 1.

Regarding the relationship between systolic BP and CV, events appear to be parallel to those for diastolic BP. That is, regardless of the in-treatment systolic BP, low achieved diastolic BP levels were associated with higher risks of the primary outcome and myocardial infarction, whereas the risk of stroke was greatest in the diabetic subjects in whom the in-treatment diastolic BP was relatively high and least in those in whom the in-treatment diastolic BP was low. This

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finding may be explained by the types of patients involved in the ONTARGET trial, in particular that about three-quarters of the patients had a history of coronary disease, with possibly a greater need for myocardial blood flow preservation (27–29).

Other characteristics of the patients with a baseline systolic BP <130 mm Hg who had an event (myocardial infarction or CV death) were significantly different from those who did not. Patients having an event had a greater probability of pre-study vascular disease (coronary or peripheral artery disease) as well as being older, being more likely to be on antidiabetic or antihypertensive treatment, and having more evidence for renal dysfunction. In contrast, there were only minimal differences between the 2 groups in either initial or achieved BP levels. Although other explanations are possible, this points to high baseline risk of the patients being a key determinant of the J-curve phenomenon, rather than a causal relationship with excessive BP reduction.

Study limitations. First, retrospective analysis of nonrandomized data might have allowed factors other than BP to influence the results. Second, the ONTARGET population was somewhat different from that usually seen in conventional hypertension trials, particularly because of their high rate of prior events. So, caution must be exercised in extrapolating these results to younger diabetic patients at lower cardiovascular risk, in whom "the lower the BP the better" rule might still apply. Third, a large proportion of patients were treated with antiplatelet therapy, β-blockers, and statins, all of which reduce CV risk. This might have minimized the potential benefit of BP-lowering strategies, particularly at the lower BP entry values. Fourth, patients categorized into groups by BP showed marked differences in other risk factors, and despite extensive adjustments for known factors, these adjustments might have been inadequate or failed to include other unknown factors. Fifth, the analysis focuses on the average of in-treatment levels of BP prior to a clinical event. It is subject to a greater degree of interpretation bias since we cannot eliminate the possibility that the BP effect on events was, in part, related to better BP control during the follow-up. Finally, the trial treatment was based on blockers of the renin-angiotensin system. It cannot be determined whether the same relationship between baseline BP, BP reductions, and changes in CV risk would hold for treatment based on other drugs.

Our data have implications for the antihypertensive treatment of diabetic patients, at least when this condition involves patients with additional high CV risks. Antihypertensive treatment should be expected to exert a clear-cut protective effect against macrovascular complications when initial systolic BP values are high. At lower initial systolic BP levels, in the 130 to 142 mm Hg range, the benefit of BP reduction mainly originates from protection against stroke. Finally, around or below an initial systolic BP of 130 mm Hg, antihypertensive treatment should be implemented with caution because of the possibility of untoward cardiac effects that could counterbalance the beneficial consequences of aggressive BP reduction for stroke. This might also apply to diastolic BP values of 67 mm Hg or less. Clearly, more evidence from prospective trials is necessary to learn whether high-risk diabetic patients with BP levels between 130 and 140 mm Hg should be treated to lower BP levels. As well, a prospective assessment of clinical markers identifying vulnerable patients in whom aggressive BP reduction could be deleterious would be of value.

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