ORIGINAL RESEARCH

Average Clinician-Measured Blood Pressures and Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus and Ischemic Heart Disease in the EXAMINE Trial

William B. White, MD; Fatima Jalil, MD; William C. Cushman, MD; George L. Bakris, MD; Richard Bergenstal, MD; Simon R. Heller, MD; Yuyin Liu, MS; Cyrus Mehta, PhD; Faiez Zannad, MD, PhD; Christopher P. Cannon, MD

Background—Blood pressure (BP) treatment goals in patients with diabetes mellitus and increased cardiovascular risk remain controversial. Our study objective was to determine cardiovascular outcomes according to achieved BPs over the average follow-up period in the EXAMINE (Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care) trial.

Methods and Results—EXAMINE was a cardiovascular outcomes trial in 5380 patients with type 2 diabetes mellitus and recent acute coronary syndromes. Risks of major adverse cardiac events and cardiovascular death or heart failure were analyzed using a Cox proportional hazards model with adjustment for baseline covariates in 10-mm Hg increments of clinician-measured systolic BP from ≤100 to >160 mm Hg and diastolic BP from ≤60 to >100 mm Hg averaged during the 24 months after randomization. Based on 2015 guidelines from the American College of Cardiology, the American Heart Association and the American Society of Hypertension and 2017 American Diabetes Association guidelines, systolic BPs of 131 to 140 mm Hg and diastolic BPs of 81 to 90 mm Hg were the reference groups. A U-shaped relationship between cardiovascular outcomes and BPs was observed. Importantly, compared with the systolic BP reference group, adjusted hazard ratios for major adverse cardiac events and cardiovascular death or heart failure were significantly higher in patients with systolic BPs <130 mm Hg. Similarly, compared with the diastolic BP reference group, adjusted hazard ratios for major adverse cardiac events and for cardiovascular death or heart failure were significantly higher for diastolic BPs <80 mm Hg.

Conclusions—In patients with type 2 diabetes mellitus and recent acute coronary syndrome, average BPs <130/80 mm Hg were associated with worsened cardiovascular outcomes. These data suggest that intensive control of BP in patients with type 2 diabetes mellitus and ischemic heart disease should be evaluated in a prospective randomized trial.

Clinical Trial Registration—URL: https://www.clinicaltrials.gov. Unique identifier: NCT00968708. (***J Am Heart Assoc*. 2018;7: e009114. DOI: 10.1161/JAHA.118.009114.)**

Key Words: blood pressure • cardiovascular outcomes • diabetes mellitus

Lowering blood pressure (BP) in patients with type 2 diabetes mellitus reduces the risk of cardiovascular events and death, but the optimal target BP has been controversial in patients with coronary artery disease.[1,2] An observational analysis of INVEST (International Verapamil SR-Trandolapril Study) in patients with type 2 diabetes mellitus showed no improvement in rates of myocardial infarction (MI) or cardiovascular death for BPs <140/90 mm Hg.[3] In

From the University of Connecticut School of Medicine, Farmington, CT (W.B.W., F.J.); Memphis Veterans Affairs Medical Center, University of Tennessee Health Science Center, Memphis, TN (W.C.C.); University of Chicago Medicine, Chicago, IL (G.L.B.); Park Nicolett Clinic, St. Louis Park, MN (R.B.); University of Sheffield, United Kingdom (S.R.H.); Baim Clinical Research Institute, Boston, MA (Y.L., C.P.C.); Harvard School of Public Health, Boston, MA (C.M.); Université de Lorraine, Nancy, France (F.Z.).

A portion of the results of this research were presented in abstract form at the American College of Cardiology scientific sessions, March 17 to 19, 2017, in Washington, DC, and at the European Association for the Study of Diabetes annual meeting, September 11 to 15, 2017, in Lisbon, Portugal.

Correspondence to: William B White, MD, Professor of Medicine, Calhoun Cardiology Center, University of Connecticut School of Medicine, 263 Farmington Avenue, Farmington, CT 06030-3940. E-mail: wwhite@uchc.edu

Received March 7, 2018; accepted August 20, 2018.

Clinical Perspective

What Is New?

- We determined cardiovascular outcomes according to clinician-achieved blood pressure (BP) levels in the EXAMINE (Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care) trial, a patient population with type 2 diabetes mellitus and recent acute coronary syndromes.
- A U-shaped relationship between cardiovascular outcomes and BPs was observed.
- Adjusted hazard ratios for both major adverse cardiac events and cardiovascular death or heart failure were significantly higher in patients with systolic BPs <130 mm Hg.
- In addition, hazard ratios for major adverse cardiac events and for cardiovascular death or heart failure were significantly higher for diastolic BPs <80 mm Hg.
- Our analysis did not support the suggestion that these findings were due to reverse causality.

What Are the Clinical Implications?

- Controversy remains regarding the target BP values in patients with hypertension and coronary artery disease.
- In the EXAMINE patients—who had both type 2 diabetes mellitus and a recent acute coronary syndrome—lowering BP to <130/80 mm Hg versus 130 to 140/80 to 89 mm Hg was associated with worsened cardiovascular outcomes.
- These data suggest that intensive BP control in patients with diabetes mellitus and ischemic heart disease should be evaluated in a prospective randomized trial that considers clinical characteristics including age and cardiac function and methodology of BP measurement.

contrast, SPRINT (Systolic Blood Pressure Interventional Trial) showed that targeting a systolic BP of <120 mm Hg in high-risk patients without type 2 diabetes mellitus was associated with a reduction in BP-related adverse outcomes, particularly heart failure and cardiovascular mortality.[4] Of note, unlike other contemporary outcome trials, BP measurements in SPRINT used a digital device and often were not attended by a clinician; these BP values are generally believed to be lower than those measured in the presence of a physician or nurse.[5]

Observational studies have shown that death due to cardiovascular disease increases progressively and linearly with BP.[6,7] However, linearity between BP and cardiovascular outcomes has been challenged by results of clinical trials. The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial showed no differences in major adverse cardiac events (MACE) at <120 mm Hg versus <140 mm Hg, although stroke rates were lower in those patients randomized to the intensive systolic BP target, and cardiovascular events were reduced by 26% in the standard glycemic intervention subgroup.[8,9] The ACCOMPLISH (Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension) trial showed that although cardiovascular benefit was observed at systolic BPs <140 mm Hg, no additional benefit occurred at lower systolic BPs.[10] In addition, in mostly nondiabetic patients with a recent acute coronary syndrome (ACS), the PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) trial showed that the lowest cardiovascular event rates were associated with mean achieved BP levels of 136/85 mm Hg.[11]

Guidelines by the American Heart Association (AHA), American College of Cardiology (ACC), and American Society of Hypertension (ASH) in 2015 recommended a BP target of <140/90 mm Hg in patients with hypertension who had a history of coronary disease.[12] Subsequently, the 2017 AHA/ACC hypertension guideline committee recommended a BP target of <130/80 mm Hg in all patients with high cardiovascular risk including those with ischemic heart disease.[13] In contrast, other guideline committees have recommended a systolic BP <140 mm Hg,[14] whereas others recommended a goal of <150 mm Hg for patients aged ≥60 years who do not have cardiovascular disease and <140 mm Hg if there is a history of stroke or cardiac diseases.[15,16] The 2018 American Diabetes Association standards of care[17] recently recommended a BP target of <140/90 mm Hg for most patients with diabetes mellitus but suggest that patients at high cardiovascular risk may benefit from a target of 130/80 mm Hg.

To address the question of a target for clinician-measured BPs in patients with diabetes mellitus and high cardiovascular risk, we evaluated the relationships among achieved clinician BPs over the average follow-up period and cardiovascular outcomes in the EXAMINE (Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care) trial,[18] a prospective, randomized, placebo-controlled trial evaluating the cardiovascular safety of the DPP-4 (dipeptidyl peptidase 4) inhibitor alogliptin in patients with type 2 diabetes mellitus and a recent ACS.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. The reason for this decision is that the publication committee is still actively working on several reports from the EXAMINE database and wishes to complete its work before making the data available for public dissemination.

Study Population and Follow-up

EXAMINE was a phase 3, multicenter, prospective, double-blind, randomized trial in which the DPP-4 inhibitor

DOI: 10.1161/JAHA.118.009114

Table 1. Demographics and Baseline Characteristics by BP Category

Characteristics	SBP Categories								*P* Value*
	≤100 mm Hg (n=49)	>100 to 110 mm Hg (n=224)	>110 to 120 mm Hg (n=851)	>120 to 130 mm Hg (n=1619)	>130 to 140 mm Hg (n=1519)	>140 to 150 mm Hg (n=731)	>150 to 160 mm Hg (n=276)	>160 mm Hg (n=111)	
Age, y	56.0 (52.0–62.0)	55.0 (49.0–63.0)	58.0 (51.0–65.0)	60.0 (53.0–67.0)	62.0 (55.0–69.0)	63.0 (57.0–70.0)	65.0 (58.0–71.0)	66.0 (60.0–74.0)	<0.001
Male sex	73.5 (36/49)	74.1 (166/224)	74.6 (635/851)	71.0 (1149/1619)	65.9 (1001/1519)	59.9 (438/731)	61.6 (170/276)	50.5 (56/111)	<0.001
Race									
American Indian or Alaska Native	4.1 (2/49)	2.2 (5/224)	2.1 (18/851)	2.3 (38/1619)	2.4 (36/1519)	0.8 (6/731)	1.4 (4/276)	0.9 (1/111)	<0.001
Asian	36.7 (18/49)	29.0 (65/224)	26.8 (228/851)	20.4 (330/1619)	17.4 (265/1519)	17.0 (124/731)	14.1 (39/276)	18.0 (20/111)	
Black or African American	6.1 (3/49)	5.4 (12/224)	3.2 (27/851)	3.4 (55/1619)	3.8 (58/1519)	4.7 (34/731)	5.1 (14/276)	11.7 (13/111)	
Native Hawaiian or other Pacific Islander	0.0 (0/49)	0.0 (0/224)	0.5 (4/851)	0.2 (4/1619)	0.0 (0/1519)	0.1 (1/731)	0.4 (1/276)	0.9 (1/111)	
White	53.1 (26/49)	62.5 (140/224)	66.3 (564/851)	72.7 (1177/1619)	75.6 (1149/1519)	76.5 (559/731)	79.0 (218/276)	68.5 (76/111)	
Multiracial	0.0 (0/49)	0.9 (2/224)	1.2 (10/851)	0.9 (15/1619)	0.7 (11/1519)	1.0 (7/731)	0.0 (0/276)	0.0 (0/111)	
BMI	26.4 (23.0–29.3)	26.6 (24.0–30.7)	27.5 (24.6–31.1)	28.5 (25.5–32.3)	29.4 (26.3–33.1)	29.7 (26.1–33.5)	30.0 (26.4–34.1)	30.0 (25.6–33.7)	<0.001
Duration of diabetes mellitus, y	5.2 (1.5–10.8)	6.0 (0.4–11.9)	6.0 (2.2–12.2)	6.6 (2.4–12.7)	6.9 (2.8–14.0)	9.6 (4.3–15.8)	10.3 (5.1–15.1)	10.2 (4.6–17.0)	<0.001
Baseline HbA1c concentration	7.6 (7.1–8.8)	8.0 (7.1–9.1)	7.9 (7.2–8.8)	7.9 (7.2–8.7)	7.8 (7.1–8.7)	8.0 (7.3–8.8)	7.9 (7.2–8.8)	7.8 (7.2–8.5)	0.184
Cardiovascular risk factors and history									
Current smoker	18.4 (9/49)	20.1 (45/224)	15.5 (132/851)	14.3 (231/1619)	12.5 (190/1519)	12.6 (92/731)	8.0 (22/276)	11.7 (13/111)	0.002
Hypertension	46.9 (23/49)	53.6 (120/224)	65.6 (558/851)	79.9 (1294/1619)	91.6 (1391/1519)	96.3 (704/731)	97.8 (270/276)	98.2 (109/111)	<0.001
Dyslipidemia	36.7 (18/49)	27.7 (62/224)	26.9 (229/851)	27.5 (445/1619)	26.1 (396/1519)	28.0 (205/731)	23.2 (64/276)	29.7 (33/111)	0.524
MI	91.8 (45/49)	95.1 (213/224)	89.7 (763/851)	87.3 (1413/1619)	87.3 (1326/1519)	87.0 (636/731)	87.3 (241/276)	87.4 (97/111)	0.026
CABG	14.3 (7/49)	8.0 (18/224)	12.0 (102/851)	13.8 (223/1619)	12.2 (185/1519)	13.3 (97/731)	15.6 (43/276)	11.7 (13/111)	0.236
PCI	57.1 (28/49)	68.3 (153/224)	65.7 (559/851)	61.1 (989/1619)	58.3 (885/1519)	67.9 (496/731)	67.8 (187/276)	67.6 (75/111)	<0.001
CHF	38.8 (19/49)	23.2 (52/224)	22.8 (194/851)	27.7 (449/1619)	33.0 (501/1519)	25.3 (185/731)	25.7 (71/276)	27.0 (30/111)	<0.001
TIA	4.1 (2/49)	0.9 (2/224)	2.1 (18/851)	2.0 (33/1619)	2.8 (43/1519)	3.7 (27/731)	6.2 (17/276)	2.7 (3/111)	0.002

Continued

Table 1. Continued

Characteristics	SBP Categories								*P* Value*
	≤100 mm Hg (n=49)	>100 to 110 mm Hg (n=224)	>110 to 120 mm Hg (n=851)	>120 to 130 mm Hg (n=1619)	>130 to 140 mm Hg (n=1519)	>140 to 150 mm Hg (n=731)	>150 to 160 mm Hg (n=276)	>160 mm Hg (n=111)	
PAD	14.3 (7/49)	7.6 (17/224)	8.5 (72/851)	7.0 (114/1619)	11.5 (174/1519)	11.1 (81/731)	12.0 (33/276)	14.4 (16/111)	<0.001
Renal function (eGFR, mL/min per 1.73 m^2)	65.8 (52.1–87.3)	75.4 (58.6–87.2)	74.8 (61.2–87.3)	72.4 (58.7–86.1)	70.9 (56.1–85.1)	68.1 (53.5–83.4)	63.4 (50.1–77.6)	61.9 (43.0–80.4)	<0.001
eGFR ≥mL/min per 1.73 m^2	63.3 (31/49)	72.8 (163/224)	77.0 (655/851)	73.5 (1190/1619)	70.6 (1073/1519)	65.8 (481/731)	58.3 (161/276)	55.0 (61/111)	<0.001
eGFR <60 mL/min per 1.73 m^2	36.7 (18/49)	27.2 (61/224)	23.0 (196/851)	26.5 (429/1619)	29.4 (446/1519)	34.2 (250/731)	41.7 (115/276)	45.0 (50/111)	<0.001
Baseline BNP concentration (pg/mL)	187.0 (44.3–579.8)	94.7 (38.6–205.7)	71.7 (29.2–165.9)	66.1 (26.2–154.3)	73.5 (29.4–161.3)	88.7 (34.8–201.4)	98.2 (38.9–210.2)	104.4 (43.8–237.9)	<0.001
Baseline cardiovascular medications									
ACEI	53.1 (26/49)	63.8 (143/224)	58.4 (497/851)	64.4 (1043/1619)	61.9 (940/1519)	62.1 (454/731)	56.9 (157/276)	56.8 (63/111)	0.037
ARB	20.4 (10/49)	14.7 (33/224)	15.7 (134/851)	19.5 (315/1619)	23.8 (361/1519)	28.2 (206/731)	31.2 (86/276)	40.5 (45/111)	<0.001
β-Blockers	75.5 (37/49)	82.1 (184/224)	80.4 (684/851)	81.0 (1312/1619)	82.8 (1257/1519)	84.7 (619/731)	83.7 (231/276)	78.4 (87/111)	0.213
Calcium channel blockers	4.1 (2/49)	7.1 (16/224)	12.9 (110/851)	19.4 (314/1619)	23.6 (359/1519)	32.0 (234/731)	38.8 (107/276)	49.5 (55/111)	<0.001
Loop diuretics	40.8 (20/49)	21.9 (49/224)	16.7 (142/851)	15.3 (248/1619)	16.9 (257/1519)	18.1 (132/731)	21.7 (60/276)	28.8 (32/111)	<0.001
Thiazide diuretics	10.2 (5/49)	6.3 (14/224)	8.5 (72/851)	13.0 (210/1619)	16.7 (253/1519)	22.0 (161/731)	22.1 (61/276)	23.4 (26/111)	<0.001
Mineralocorticoid blockers	36.7 (18/49)	20.1 (45/224)	16.6 (141/851)	12.7 (205/1619)	10.7 (162/1519)	9.7 (71/731)	11.6 (32/276)	5.4 (6/111)	<0.001
Baseline antihyperglycemic medications									
Insulin	20.4 (10/49)	26.8 (60/224)	27.7 (236/851)	28.0 (453/1619)	28.4 (431/1519)	36.0 (263/731)	39.5 (109/276)	38.7 (43/111)	<0.001
Sulfonylureas	40.8 (20/49)	46.0 (103/224)	48.9 (416/851)	46.2 (748/1619)	48.4 (735/1519)	45.3 (331/731)	39.5 (109/276)	36.9 (41/111)	0.039
Metformin	71.4 (35/49)	63.4 (142/224)	70.4 (599/851)	66.8 (1082/1619)	64.4 (978/1519)	64.7 (473/731)	65.6 (181/276)	64.9 (72/111)	0.120
Thiazolidinediones	2.0 (1/49)	2.2 (5/224)	2.4 (20/851)	3.0 (48/1619)	2.2 (33/1519)	1.9 (14/731)	2.9 (8/276)	1.8 (2/111)	0.812
BP parameters									
Mean SBP (mm Hg)	98.0 (94.0–99.5)	107.0 (105.0–109.4)	116.7 (114.3–119.0)	125.6 (123.2–128.0)	134.7 (132.3–136.8)	144.0 (142.0146.6)	153.9 (151.8–156.9)	166.6 (162.7–174.3)	<0.001
Mean DBP (mm Hg)	62.1 (60.0–67.0)	68.3 (63.9–71.0)	72.8 (69.5–76.7)	76.9 (72.7–80.0)	80.0 (75.5–83.1)	81.9 (76.5–86.0)	82.2 (76.9–88.1)	84.5 (78.0–91.8)	<0.001

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DOI: 10.1161/JAHA.118.009114

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Table 1. Continued

Characteristics	SBP Categories								*P* Value*
	≤100 mm Hg (n=49)	>100 to 110 mm Hg (n=224)	>110 to 120 mm Hg (n=851)	>120 to 130 mm Hg (n=1619)	>130 to 140 mm Hg (n=1519)	>140 to 150 mm Hg (n=731)	>150 to 160 mm Hg (n=276)	>160 mm Hg (n=111)	
Randomization group									
Placebo	49.0 (24/49)	48.2 (108/224)	43.8 (373/851)	50.3 (815/1619)	51.0 (774/1519)	52.4 (383/731)	55.1 (152/276)	45.0 (50/111)	0.007
Alogliptin	51.0 (25/49)	51.8 (116/224)	56.2 (478/851)	49.7 (804/1619)	49.0 (745/1519)	47.6 (348/731)	44.9 (124/276)	55.0 (61/111)	

Characteristics	DBP Categories						*P* Value†
	≤60 mm Hg (n=117)	>60 to 70 mm Hg (n=836)	>70 to 80 mm Hg (n=2635)	>80 to 90 mm Hg (n=1617)	>90 to 100 mm Hg (n=157)	>100 mm Hg (n=18)	
Age, y	68.0 (62.0–74.0)	65.0 (57.0–71.0)	61.0 (54.0–68.0)	59.0 (53.0–65.0)	56.0 (50.0–65.0)	54.0 (45.0–58.0)	<0.001
Male sex	49.6 (58/117)	64.7 (541/836)	69.5 (1832/2635)	67.8 (1097/1617)	70.7 (111/157)	66.7 (12/18)	<0.001
Race							
American Indian or Alaska Native	4.3 (5/117)	2.2 (18/836)	1.5 (39/2635)	2.8 (45/1617)	1.9 (3/157)	0.0 (0/18)	<0.001
Asian	23.1 (27/117)	22.2 (186/836)	21.1 (555/2635)	17.4 (282/1617)	22.9 (36/157)	16.7 (3/18)	
Black or African American	2.6 (3/117)	4.9 (41/836)	2.9 (77/2635)	4.5 (72/1617)	14.0 (22/157)	5.6 (1/18)	
Native Hawaiian or other Pacific Islander	0.0 (0/117)	0.2 (2/836)	0.2 (4/2635)	0.2 (4/1617)	0.0 (0/157)	5.6 (1/18)	
White	70.1 (82/117)	69.4 (580/836)	73.5 (1937/2635)	74.3 (1201/1617)	61.1 (96/157)	72.2 (13/18)	
Multiracial	0.0 (0/117)	1.1 (9/836)	0.9 (23/2635)	0.8 (13/1617)	0.0 (0/157)	0.0 (0/18)	
BMI	27.5 (22.7–31.8)	27.6 (24.7–31.6)	28.4 (25.3–32.0)	29.7 (26.6–33.7)	30.5 (27.0–34.4)	32.7 (28.9–36.2)	<0.001
Duration of diabetes mellitus, y	13.5 (7.6–22.1)	9.6 (3.7–16.8)	7.3 (2.8–13.7)	6.1 (2.3–11.2)	5.5 (2.1–10.6)	1.9 (0.1–5.1)	<0.001
Baseline HbA1c concentration	7.7 (7.3–8.6)	7.8 (7.1–8.6)	7.9 (7.2–8.7)	7.9 (7.2–8.8)	8.0 (7.1–8.9)	7.7 (7.1–8.5)	0.153
Cardiovascular risk factors and history							
Current smoker	6.8 (8/117)	13.8 (115/836)	13.6 (358/2635)	13.8 (223/1617)	17.8 (28/157)	11.1 (2/18)	0.214
Hypertension	82.9 (97/117)	74.5 (623/836)	80.7 (2127/2635)	89.9 (1453/1617)	97.5 (153/157)	88.9 (16/18)	<0.001
Dyslipidemia	27.4 (32/117)	30.0 (251/836)	26.2 (690/2635)	26.5 (428/1617)	29.3 (46/157)	27.8 (5/18)	0.366
MI	91.5 (107/117)	88.8 (742/836)	87.6 (2309/2635)	87.6 (1416/1617)	91.7 (144/157)	88.9 (16/18)	0.484
CABG	26.5 (31/117)	16.1 (135/836)	12.6 (332/2635)	10.9 (176/1617)	7.6 (12/157)	11.1 (2/18)	<0.001
PCI	66.7 (78/117)	67.9 (568/836)	63.0 (1660/2635)	58.8 (951/1617)	64.3 (101/157)	77.8 (14/18)	<0.001

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DOI: 10.1161/JAHA.118.009114

Table 1. Continued

Characteristics	DBP Categories						*P* Value†
	≤60 mm Hg (n=117)	>60 to 70 mm Hg (n=836)	>70 to 80 mm Hg (n=2635)	>80 to 90 mm Hg (n=1617)	>90 to 100 mm Hg (n=157)	>100 mm Hg (n=18)	
CHF	34.2 (40/117)	27.2 (227/836)	26.1 (688/2635)	31.0 (502/1617)	26.8 (42/157)	11.1 (2/18)	0.004
TIA	3.4 (4/117)	3.1 (26/836)	2.7 (70/2635)	2.5 (40/1617)	3.2 (5/157)	0.0 (0/18)	0.884
PAD	22.2 (26/117)	12.2 (102/836)	8.5 (225/2635)	9.0 (145/1617)	8.9 (14/157)	11.1 (2/18)	<0.001
Renal function (eGFR, mL/min per 1.73 m^2)	57.7 (41.2–71.5)	66.9 (53.6–83.6)	71.3 (57.1–85.4)	74.2 (59.6–86.7)	74.5 (55.8–88.3)	67.3 (55.8–85.6)	<0.001
eGFR ≥60 mL/min per 1.73 m^2	46.2 (54/117)	64.0 (535/836)	72.1 (1899/2635)	74.5 (1205/1617)	70.7 (111/157)	61.1 (11/18)	<0.001
eGFR <60 mL/min per 1.73 m^2	53.8 (63/117)	36.0 (301/836)	27.9 (736/2635)	25.5 (412/1617)	29.3 (46/157)	38.9 (7/18)	<0.001
Baseline BNP concentration (pg/mL)	121.1 (57.0–273.8)	98.7 (42.3–203.6)	72.4 (29.4–162.7)	68.0 (24.7–161.0)	71.2 (28.5–182.4)	25.1 (9.0–144.3)	<0.001
Baseline cardiovascular medications							
ACEI	57.3 (67/117)	59.0 (493/836)	61.6 (1622/2635)	64.1 (1037/1617)	60.5 (95/157)	50.0 (9/18)	0.117
ARB	25.6 (30/117)	22.2 (186/836)	22.0 (579/2635)	21.2 (342/1617)	29.3 (46/157)	38.9 (7/18)	0.094
β-Blockers	81.2 (95/117)	82.1 (686/836)	82.0 (2162/2635)	81.8 (1322/1617)	82.8 (130/157)	88.9 (16/18)	0.979
Calcium channel blockers	28.2 (33/117)	21.5 (180/836)	20.1 (529/2635)	24.7 (399/1617)	30.6 (48/157)	44.4 (8/18)	<0.001
Loop diuretics	35.0 (41/117)	24.6 (206/836)	17.1 (450/2635)	13.5 (218/1617)	14.0 (22/157)	16.7 (3/18)	<0.001
Thiazide diuretics	20.5 (24/117)	12.1 (101/836)	13.9 (367/2635)	17.3 (280/1617)	16.6 (26/157)	22.2 (4/18)	0.002
Mineralocorticoid blockers	19.7 (23/117)	16.5 (138/836)	12.3 (325/2635)	10.7 (173/1617)	12.1 (19/157)	11.1 (2/18)	<0.001
Baseline antihyperglycemic medications							
Insulin	44.4 (52/117)	34.2 (286/836)	29.3 (773/2635)	27.8 (449/1617)	27.4 (43/157)	11.1 (2/18)	<0.001
Sulfonylureas	36.8 (43/117)	44.3 (370/836)	47.1 (1242/2635)	47.5 (768/1617)	47.8 (75/157)	27.8 (5/18)	0.079
Metformin	51.3 (60/117)	65.4 (547/836)	67.5 (1779/2635)	65.7 (1062/1617)	65.0 (102/157)	66.7 (12/18)	0.014

Continued

Table 1. Continued

Characteristics	DBP Categories						P Value†
	≤60 mm Hg (n=117)	>60 to 70 mm Hg (n=836)	>70 to 80 mm Hg (n=2635)	>80 to 90 mm Hg (n=1617)	>90 to 100 mm Hg (n=157)	>100 mm Hg (n=18)	
Thiazolidinediones	2.6 (3/117)	3.5 (29/836)	2.6 (69/2635)	1.5 (25/1617)	3.2 (5/157)	0.0 (0/18)	0.066
BP parameters							
Mean SBP (mm Hg)	116.7 (106.3–127.2)	120.8 (112.6–130.2)	127.5 (121.0–134.8)	135.4 (130.0–142.5)	148.0 (141.7–155.7)	159.7 (153.0–165.7)	<0.001
Mean DBP (mm Hg)	58.2 (56.0–59.6)	67.5 (65.0–69.3)	76.1 (73.6–78.3)	83.3 (81.6–85.6)	92.8 (91.5–95.1)	104.5 (102.0109.0)	<0.001
Randomization group							
Placebo	53.8 (63/117)	47.7 (399/836)	49.3 (1300/2635)	51.1 (827/1617)	52.2 (82/157)	44.4 (8/18)	0.524
Alogliptin	46.2 (54/117)	52.3 (437/836)	50.7 (1335/2635)	48.9 (790/1617)	47.8 (75/157)	55.6 (10/18)	

For continuous variables, mean and interquartile ranges are presented; otherwise, data are shown as percentage (frequency). ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; CHF, congestive heart failure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TIA, transient ischemic attack.

*P values are based on 1-way ANOVA for continuous variables and Pearson χ^2 test for the categorical variables.

†P values are based on 1-way ANOVA for continuous variables and Pearson χ^2 test for the remaining categorical variables.

alogliptin was compared with placebo regarding cardiovascular outcomes in 5380 patients with type 2 diabetes mellitus and a well-defined ACS event 15 to 90 days before randomization.[17] Patients were eligible for enrollment if they had a diagnosis of type 2 diabetes mellitus, were receiving antidiabetic therapy (with the exception of a DPP-4 inhibitor or GLP-1 [glucagon-like peptide 1] analog), and had a history of ACS within 15 to 90 days before randomization. Further criteria for type 2 diabetes mellitus included glycated hemoglobin between 6.5% and 11.0%, inclusive, at screening, but if the antidiabetic regimen included insulin, the patient was required to have glycated hemoglobin between 7.0% and 11.0%. ACS included diagnoses of acute MI or hospitalization with unstable angina. Major exclusion criteria included a diagnosis of type 1 diabetes mellitus; unstable cardiac disorders, such as New York Heart Association class 4 heart failure, refractory angina, uncontrolled arrhythmias, critical valvular heart disease, or severe uncontrolled hypertension; and dialysis within 14 days of screening. The EXAMINE trial was approved by regional institutional review boards, and participants gave informed consent before any study-related procedure was initiated.

The primary results demonstrated comparable cardiovascular outcomes for the DPP-4 inhibitor alogliptin and placebo. Patients in EXAMINE were followed for up to 40 months (median duration: 18 months). Patients were assessed at 1, 3, 6, 9, and 12 months after randomization during the first year of the study and every 4 months during subsequent years of participation. BPs were measured in the seated position in duplicate at every visit by clinicians according to AHA recommendations.[19] The EXAMINE protocol advocated that control of all cardiovascular risk factors, including hypertension, be maintained according to evidence-based standards for participating countries and investigative sites.

Study Outcomes

Cardiovascular outcomes

Primary and secondary outcome measures in the present analysis were the same as those described in the primary trial results.[18] The primary end point was a composite of death due to cardiovascular causes, nonfatal MI, and nonfatal stroke. Other major end points included a composite of cardiovascular mortality or hospitalization for heart failure and all-cause mortality or hospitalization for heart failure.[19,20] Cardiovascular events were prospectively adjudicated by an end points committee (C5, Cleveland Clinic, Cleveland, Ohio) blinded to treatment assignment.

Table 2. Major Adverse Cardiovascular Events Through 24 Months by BP Category

SBP Group (mm Hg)	Total Patients	Corresponding DBP (mm Hg), Mean±SD	Incidence Rate, n (%)	Average Follow-up SBP, Adjusted HR (95% CI)	Baseline SBP, Adjusted HR (95% CI)
≤100	49	62.8±5.5	11 (26.5)	43.7 (18.0–106.0)	6.0 (3.1–11.7)
>100 to 110	224	67.8±6.4	46 (25.2)	18.0 (10.2–31.7)	4.2 (2.9–6.0)
>110 to 120	851	72.6±5.7	78 (11.5)	3.8 (2.5–5.7)	1.5 (1.1–2.0)
>120 to 130	1619	76.0±5.8	150 (11.3)	1.8 (1.4–2.4)	1.1 (0.9–1.4)
>130 to 140	1519	79.1±6.2	146 (12.1)	Reference	Reference
>140 to 150	731	81.1±7.7	80 (13.3)	0.6 (0.4–0.8)	0.9 (0.7–1.2)
>150 to 160	276	82.2±8.6	55 (25.0)	0.5 (0.3–0.8)	1.5 (1.1–2.1)
>160	111	85.2±11.2	28 (35.9)	0.2 (0.1–0.5)	1.7 (1.1–2.6)
DBP Group (mm Hg)	**Total Patients**	**SBP (mm Hg), Mean±SD**	**Incidence Rate, n (%)**	**Average Follow-up DBP, Adjusted HR (95% CI)**	**Baseline DBP, Adjusted HR (95% CI)**
≤60	117	118.2±16.0	37 (36.3)	38.4 (15.9–93.0)	4.0 (2.7–6.1)
>60 to 70	836	122.5±14.2	133 (19.3)	8.5 (4.8–15.0)	2.0 (1.5–2.7)
>70 to 80	2635	128.6±11.0	251 (11.8)	2.1 (1.6–3.0)	1.1 (0.9–1.3)
>80 to 90	1617	136.8±10.6	146 (11.6)	Reference	Reference
>90 to 100	157	149.1±11.9	24 (20.0)	0.8 (0.5–1.4)	1.9 (1.2–3.0)
>100	18	163.7±19.3	3 (21.6)	0.2 (0.1–1.0)	1.7 (0.5–5.3)

BP indicates blood pressure; CI, confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; SBP, systolic blood pressure.

Statistical Analysis

The risk of cardiovascular events was analyzed using a Cox proportional hazards model with adjustment for baseline covariates in 10-mm Hg increments of clinic systolic BPs from ≤100 to >160 mm Hg and diastolic BPs from ≤60 to >100 mm Hg averaged during the postrandomization period. Based on the 2015 ACC/AHA/ASH guideline for the treatment of hypertension in patients with ischemic heart disease,[12] systolic BPs of 131 to 140 mm Hg and diastolic BPs of 81 to 90 mm Hg were chosen as the reference groups.

Cox proportional hazards analysis was performed to assess the risk of outcomes for each 10-mm Hg increment or decrement in BP. The analysis included BP category as the major factor, with adjustments for age, sex, smoking, baseline body mass index, history of hypertension, duration and treatment of diabetes mellitus, history of coronary artery bypass grafting surgery, coronary angioplasty, angina pectoris, cerebrovascular disease, congestive heart failure, peripheral arterial disease, estimated glomerular filtration rate, transient ischemic attack, angiotensin receptor blockers, diuretics, and aspirin effect. The whole EXAMINE cohort and the 2 randomized treatment groups separately followed the same BP and event patterns, so the entire cohort was analyzed.

Models were created using baseline BP and average on-treatment follow-up BPs. BP measurements were included only before the first event (MACE, death, hospitalized heart failure, MI, stroke) for the average follow-up BP calculation. Consequently, even if they are not baseline measurements, they were still considered as "baseline" as the BPs were taken before the event. The average follow-up BP represents the effect of BP control over a period of time rather than at 1 point in time; this was considered to be a superior way of predicting long-term events and was used for the development of cubic spline analyses. We hypothesized that if a J- or U-shaped relationship was found with both baseline and average follow-up BP variables and outcomes, it was likely due to reverse causality (with low BP being representative of poor prognosis). If, however, a J- or U-shaped relationship was found with average clinician BPs but not with baseline BPs, the BP itself was more likely to contribute to increased events at follow-up. In addition, baseline, average mean, and final BPs as well as the number of BPs were calculated in those study patients who had a nonfatal cardiovascular event or who died versus those who did not die or who did not have a nonfatal cardiovascular event. Patients were censored at the point of death if they did not have a prior nonfatal event of interest. All analyses were performed using SAS version 9.4 (SAS Institute) and were performed by the biometrics group at the Baim Clinical Research Institute (Boston, Massachusetts).

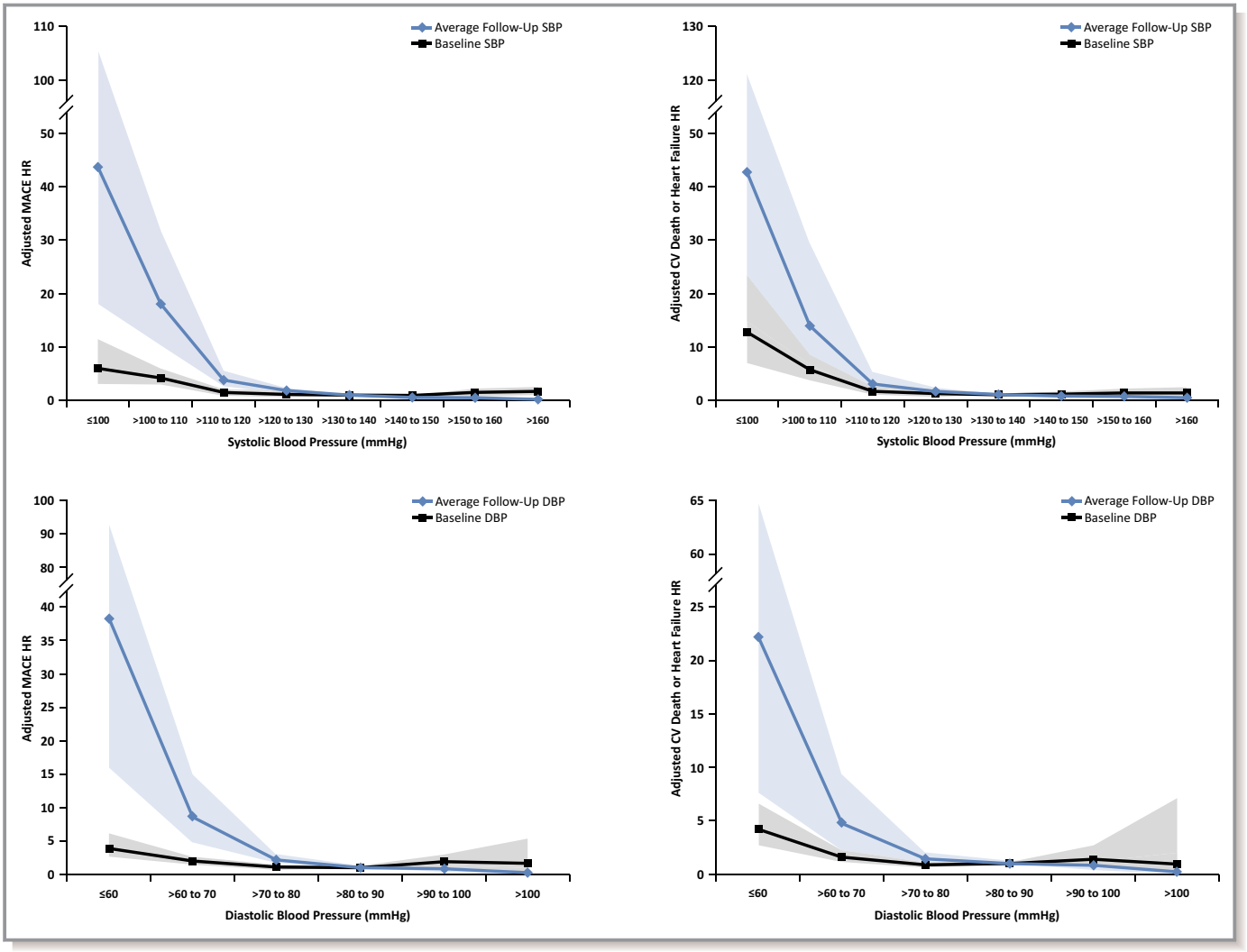

Figure 1. Achieved and baseline blood pressures (BPs) and cardiovascular outcomes. Upper panels show baseline and achieved systolic BP (SBP) and major adverse cardiac events (MACE) and cardiovascular (CV) death or heart failure. Lower panels show baseline and achieved diastolic BP (DBP) and MACE or CV death and heart failure. Shaded areas represent the upper and lower 95% confidence limits for the hazard ratios (HRs).

Results

Baseline Patients Characteristics

The baseline characteristics according to the systolic and diastolic BP categories are shown in Table 1. Higher categories of systolic BP were associated with older age, whereas higher categories of diastolic BP were associated with younger age. Higher systolic and diastolic BPs were associated with higher body mass index. In addition, the duration of diabetes mellitus was longer in patients with higher systolic BP and lower in patients with higher diastolic BP. Kidney function was lower in patients with the highest levels of systolic and diastolic BP; history of heart failure and baseline BNP (brain natriuretic peptide) levels were highest in those patients with low systolic and diastolic BP at baseline. Corresponding to these findings was higher use of diuretics and mineralocorticoid receptor antagonists in patients with lower systolic and diastolic BPs. Of note, use of insulin was more common in patients who had higher baseline systolic BP and lower levels of baseline diastolic BP.

BP and MACE (Primary End Point)

After adjustment for baseline covariates compared with the systolic BP reference group (systolic BP 131–140 mm Hg), the risk of the primary outcome increased significantly in the groups with achieved clinician average follow-up systolic BPs <130 mm Hg and those patients whose baseline systolic BPs were <120 mm Hg or >160 mm Hg (Table 2, Figure 1). The risk of the primary outcome was also significantly greater in those patients whose achieved clinician average

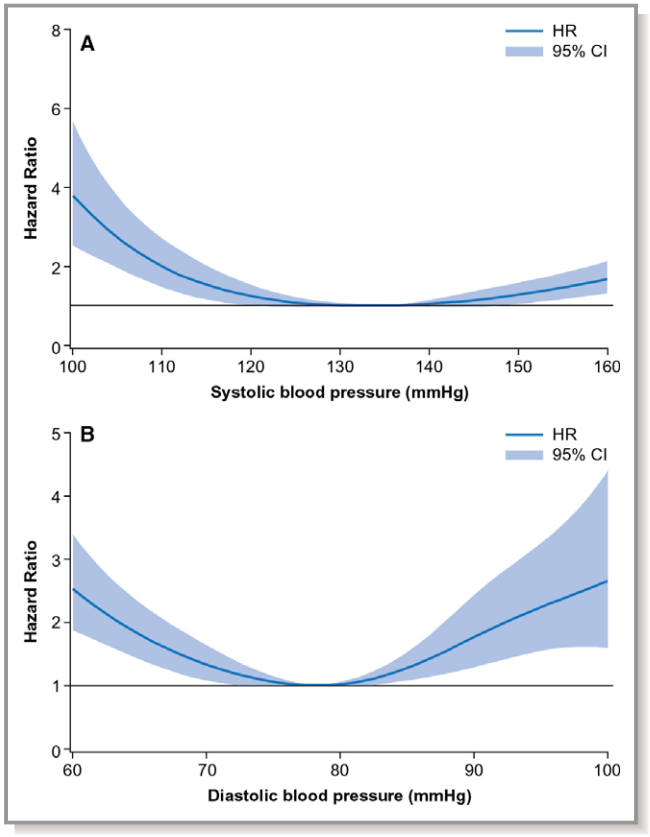

Figure 2. Cubic spline curves depicting the relationship between average clinician blood pressure and the hazard ratio for the primary end point in EXAMINE (composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke). Upper panel depicts systolic blood pressure; lower panel shows diastolic blood pressure. The lowest event rates occurred at systolic blood pressures of 132 to 136 mm Hg and at diastolic blood pressures of 77 to 80 mm Hg. CI indicates confidence interval; EXAMINE, Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care; HR, hazard ratio.

follow-up diastolic BPs were ≤71 to 80 mm Hg compared with the reference group (diastolic BP 81–90 mm Hg; Table 2, Figure 1). Similar results were observed when the diastolic BP was ≤61 to 70 mm Hg at baseline. There were too few events in the group with the highest levels of diastolic BP to evaluate outcomes. A J-shaped relationship was demonstrated for the achieved average follow-up systolic BP but not with the baseline systolic and diastolic BPs (Figure 1).

As shown in Figure 2, restricted cubic spline curves showed a U-shaped relationship between the achieved average follow-up clinician BP and the hazard ratio for the primary end point in EXAMINE, particularly for the diastolic BP. Adjusted hazard rates for the composite of cardiovascular death, nonfatal MI, and nonfatal stroke were higher for systolic BPs >135 or <135 mm Hg and for diastolic BPs >78 or <78 mm Hg.

BP and Other Cardiovascular Outcomes

The risk of the composite of cardiovascular death or heart failure was significantly greater in patients whose achieved average follow-up systolic BP was ≤121 to 130 mm Hg compared with the reference group (131–140 mm Hg); for baseline systolic BPs, the hazard ratio was greater for values of ≤111 to 120 mm Hg (Table 3). The risk of the composite of cardiovascular death or heart failure also was significantly greater in patients with average follow-up diastolic BP of ≤71 to 80 mm Hg compared with the reference group (81–90 mm Hg) and in the group with baseline diastolic BP between ≤61 and 70 mm Hg compared with the reference group (Table 3). A more pronounced J-shaped relationship was demonstrated for the achieved average follow-up systolic and diastolic BPs than with the baseline systolic BP (Figure 1).

All-cause mortality results are shown in Table 4. The hazard ratios were significantly greater for average follow-up systolic BPs of ≤111 to 120 mm Hg than the reference group and for average follow-up diastolic BPs of ≤71 to 80 mm Hg compared with the reference group. Similar trends were found for the baseline BP levels and all-cause mortality.

The relationship between achieved average follow-up and baseline BPs and nonfatal MI (Table 5) show similar trends for the primary end point. Achieved average follow-up systolic BPs of ≤121 to 130 mm Hg and diastolic BPs of ≤71 to 80 mm Hg have significantly higher adjusted hazard ratios for MI compared with the reference group. Baseline systolic BPs >150 mm Hg were also associated with an increased risk of nonfatal MI compared with the reference group, but this was not observed with the achieved average follow-up systolic BPs.

Hospitalization for heart failure alone and cardiovascular death alone (Tables 6 and 7) also showed higher hazard ratios for achieved average clinician systolic BPs of ≤121 to 130 mm Hg compared with the reference and for diastolic BPs of ≤61 to 70 mm Hg compared with the reference group. Event rates for nonfatal stroke were low; therefore, relationship between the BP levels and stroke outcomes could not be meaningfully assessed (Table 8).

BPs at baseline, averaged over the entire study period, and at the last visit of the trial (or if censored because of death or study discontinuation related to an event) were similar in those patients who did versus did not have a nonfatal MI or stroke (Table 9), who did versus did not have a hospitalization for heart failure (Table 10), or who lived versus sustained a cardiovascular death during the trial (Table 11). In addition, the median follow-up in the trial was comparable for those who did versus did not have a nonfatal event.

Table 3. Cardiovascular Death or Heart Failure Hospitalization Through 24 Months by BP Category

SBP Group (mm Hg)	Total Patients	DBP (mm Hg), Mean±SD	Incidence Rate, n (%)	Average Follow-up SBP, Adjusted HR (95% CI)	Baseline SBP, Adjusted HR (95% CI)
≤100	49	62.8±5.5	16 (42.4)	42.6 (14.9–121.8)	12.7 (6.9–23.5)
>100 to 110	224	67.8±6.4	41 (21.6)	13.9 (6.5–29.5)	5.7 (3.7–8.6)
>110 to 120	851	72.6±5.7	57 (8.4)	3.0 (1.8–5.3)	1.7 (1.2–2.5)
>120 to 130	1619	76.0±5.8	93 (7.3)	1.6 (1.1–2.3)	1.2 (0.9–1.6)
>130 to 140	1519	79.1±6.2	82 (6.9)	Reference	Reference
>140 to 150	731	81.1±7.7	52 (8.9)	0.8 (0.5–1.2)	1.1 (0.8–1.6)
>150 to 160	276	82.2±8.6	28 (12.8)	0.8 (0.4–1.4)	1.4 (1.0–2.3)
>160	111	85.2±11.2	12 (15.8)	0.4 (0.1–1.2)	1.3 (0.7–2.5)
DBP Group (mm Hg)	**Total Patients**	**SBP (mm Hg), Mean±SD**	**Incidence Rate, n (%)**	**Average Follow-up DBP, Adjusted HR (95% CI)**	**Baseline DBP, Adjusted HR (95% CI)**
≤60	117	118.2±16.0	36 (38.3)	22.3 (7.7–64.5)	4.2 (2.7–6.7)
>60 to 70	836	122.5±14.2	90 (13.6)	4.7 (2.3–9.5)	1.6 (1.2–2.3)
>70 to 80	2635	128.6±11.0	144 (6.8)	1.4 (1.0–2.1)	0.9 (0.7–1.1)
>80 to 90	1617	136.8±10.6	98 (7.7)	Reference	Reference
>90 to 100	157	149.1±11.9	12 (10.6)	0.8 (0.4–1.6)	1.4 (0.8–2.7)
>100	18	163.7±19.3	1 (5.6)	0.2 (0.0–2.0)	0.9 (0.1–7.1)

BP indicates blood pressure; CI, confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; SBP, systolic blood pressure.

Discussion

The primary results of our BP analysis in patients with diabetes mellitus and ischemic heart disease from the EXAMINE trial showed that rates of the primary end point (MACE) were increasingly higher as systolic BPs fell <130 mm Hg and diastolic BPs fell <80 mm Hg compared with the reference range of 131 to 140/81 to 90 mm Hg.[12]

Table 4. All-Cause Mortality Through 24 Months by BP Category

SBP Group (mm Hg)	Total Patients	DBP (mm Hg), Mean±SD	Incidence Rate, n (%)	Average Follow-up SBP, Adjusted HR (95% CI)	Baseline SBP, Adjusted HR (95% CI)
≤100	49	62.8±5.5	12 (32.1)	34.2 (10.6–110.0)	12.5 (6.1–25.4)
>100 to 110	224	67.8±6.4	31 (17.4)	11.9 (5.2–27.2)	5.6 (3.5–9.0)
>110 to 120	851	72.6±5.7	42 (6.5)	2.8 (1.5–5.1)	1.7 (1.1–2.6)
>120 to 130	1619	76.0±5.8	64 (5.1)	1.3 (0.9–1.9)	1.0 (0.7–1.4)
>130 to 140	1519	79.1±6.2	69 (5.9)	Reference	Reference
>140 to 150	731	81.1±7.7	39 (7.2)	0.7 (0.5–1.2)	0.9 (0.6–1.4)
>150 to 160	276	82.2±8.6	20 (9.1)	0.7 (0.3–1.4)	1.2 (0.7–2.0)
>160	111	85.2±11.2	13 (17.3)	0.5 (0.1–1.7)	1.5 (0.8–3.0)
DBP Group (mm Hg)	**Total Patients**	**SBP (mm Hg), Mean±SD**	**Incidence Rate, n (%)**	**Average Follow-up DBP, Adjusted HR (95% CI)**	**Baseline DBP, Adjusted HR (95% CI)**
≤60	117	118.2±16.0	27 (29.7)	20.5 (6.0–69.7)	5.4 (3.2–9.2)
>60 to 70	836	122.5±14.2	67 (10.2)	4.7 (2.1–10.5)	2.0 (1.4–3.0)
>70 to 80	2635	128.6±11.0	120 (6.0)	1.6 (1.0–2.6)	1.1 (0.8–1.5)
>80 to 90	1617	136.8±10.6	68 (5.5)	Reference	Reference
>90 to 100	157	149.1±11.9	8 (7.1)	0.9 (0.4–2.0)	1.4 (0.7–2.9)
>100	18	163.7±19.3	0 (0.0)	–	–

BP indicates blood pressure; CI, confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; SBP, systolic blood pressure.

Table 5. Nonfatal MI Through 24 Months by BP Category

SBP Group (mm Hg)	Total Patients	DBP (mm Hg), Mean±SD	Incidence Rate, n (%)	Average Follow-up SBP, Adjusted HR (95% CI)	Baseline SBP, Adjusted HR (95% CI)
≤100	49	62.8±5.5	2 (5.8)	6.8 (1.4–33.0)	1.8 (0.4–7.4)
>100 to 110	224	67.8±6.4	27 (15.5)	10.6 (5.4–20.8)	3.9 (2.4–6.2)
>110 to 120	851	72.6±5.7	50 (7.5)	2.9 (1.8–4.7)	1.5 (1.0–2.2)
>120 to 130	1619	76.0±5.8	89 (7.0)	1.5 (1.1–2.1)	1.1 (0.8–1.5)
>130 to 140	1519	79.1±6.2	88 (7.5)	Reference	Reference
>140 to 150	731	81.1±7.7	47 (7.6)	0.6 (0.4–1.0)	0.9 (0.7–1.3)
>150 to 160	276	82.2±8.6	34 (15.6)	0.7 (0.4–1.2)	1.5 (1.0–2.3)
>160	111	85.2±11.2	17 (23.7)	0.4 (0.1–1.0)	1.7 (1.0–3.0)
DBP Group (mm Hg)	Total Patients	SBP (mm Hg), Mean±SD	Incidence Rate, n (%)	Average Follow-up DBP, Adjusted HR (95% CI)	Baseline DBP, Adjusted HR (95% CI)
≤60	117	118.2±16.0	22 (23.7)	32.1 (10.3–100.5)	3.8 (2.2–6.5)
>60 to 70	836	122.5±14.2	84 (12.2)	8.1 (3.9–17.0)	2.1 (1.4–3.0)
>70 to 80	2635	128.6±11.0	153 (7.4)	2.2 (1.4–3.3)	1.2 (0.9–1.5)
>80 to 90	1617	136.8±10.6	82 (6.7)	Reference	Reference
>90 to 100	157	149.1±11.9	11 (9.7)	0.7 (0.3–1.5)	1.6 (0.8–3.0)
>100	18	163.7±19.3	2 (15.6)	0.3 (0.1–1.5)	1.9 (0.4–7.5)

BP indicates blood pressure; CI, confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; MI, myocardial infarction; SBP, systolic blood pressure.

Similar results were observed for the composite of cardiovascular death or hospitalization for heart failure and the individual events of all-cause mortality, non-fatal MI, and hospitalization for heart failure. The degree of risk was notably greater for those who had achieved average follow-up BPs of <120/70 mm Hg. Rates of MACE, including mortality, were lowest in patients whose pressures were maintained at a nadir of 135/78 mm Hg. Consequently, both lower systolic

Table 6. Hospitalized Heart Failure Through 24 Months by BP Category

SBP Group (mm Hg)	Total Patients	DBP (mm Hg), Mean±SD	Incidence Rate, n (%)	Average Follow-up SBP, Adjusted HR (95% CI)	Baseline SBP, Adjusted HR (95% CI)
≤100	49	62.8±5.5	9 (25.7)	33.7 (6.9–165.7)	10.1 (4.4–23.2)
>100 to 110	224	67.8±6.4	21 (11.4)	11.5 (3.7–36.3)	4.9 (2.7–8.9)
>110 to 120	851	72.6±5.7	35 (5.3)	3.4 (1.5–7.6)	1.9 (1.2–3.1)
>120 to 130	1619	76.0±5.8	44 (3.5)	1.5 (0.9–2.7)	1.1 (0.8–1.8)
>130 to 140	1519	79.1±6.2	36 (3.0)	Reference	Reference
>140 to 150	731	81.1±7.7	25 (4.2)	0.9 (0.5–1.8)	1.3 (0.8–2.1)
>150 to 160	276	82.2±8.6	17 (7.7)	1.1 (0.4–2.8)	2.0 (1.1–3.7)
>160	111	85.2±11.2	4 (3.8)	0.3 (0.0–2.2)	1.1 (0.4–3.1)
DBP Group (mm Hg)	Total Patients	SBP (mm Hg), Mean±SD	Incidence Rate, n (%)	Average Follow-up DBP, Adjusted HR (95% CI)	Baseline DBP, Adjusted HR (95% CI)
≤60	117	118.2±16.0	20 (23.3)	22.7 (5.1–101.1)	3.2 (1.7–6.0)
>60 to 70	836	122.5±14.2	48 (7.4)	4.8 (1.8–12.9)	1.3 (0.8–2.1)
>70 to 80	2635	128.6±11.0	68 (3.2)	1.3 (0.8–2.4)	0.7 (0.5–1.1)
>80 to 90	1617	136.8±10.6	48 (3.8)	Reference	Reference
>90 to 100	157	149.1±11.9	6 (5.1)	0.7 (0.3–2.0)	1.5 (0.6–3.5)
>100	18	163.7±19.3	1 (5.6)	0.4 (0.0–3.8)	2.0 (0.3–14.4)

BP indicates blood pressure; CI, confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; SBP, systolic blood pressure.

Table 7. Cardiovascular Death Through 24 Months by BP Category

SBP Group (mm Hg)	Total Patients	DBP (mm Hg), Mean±SD	Incidence Rate, n (%)	Average Follow-up SBP, Adjusted HR (95% CI)	Baseline SBP, Adjusted HR (95% CI)
≤100	49	62.8±5.5	8 (20.8)	46.1 (12.0–176.7)	11.4 (4.9–26.8)
>100 to 110	224	67.8±6.4	23 (12.6)	15.8 (6.2–40.4)	5.6 (3.2–9.7)
>110 to 120	851	72.6±5.7	27 (4.0)	2.9 (1.4–5.8)	1.5 (0.9–2.4)
>120 to 130	1619	76.0±5.8	53 (4.1)	1.6 (1.0–2.4)	1.1 (0.7–1.6)
>130 to 140	1519	79.1±6.2	54 (4.6)	Reference	Reference
>140 to 150	731	81.1±7.7	31 (5.7)	0.7 (0.4–1.1)	0.9 (0.6–1.5)
>150 to 160	276	82.2±8.6	15 (7.1)	0.5 (0.2–1.2)	1.2 (0.7–2.1)
>160	111	85.2±11.2	9 (12.9)	0.3 (0.1–1.2)	1.4 (0.6–3.0)
DBP Group (mm Hg)	**Total Patients**	**SBP (mm Hg), Mean±SD**	**Incidence Rate, n (%)**	**Average Follow-up DBP, Adjusted HR (95% CI)**	**Baseline DBP, Adjusted HR (95% CI)**
≤60	117	118.2±16.0	20 (21.1)	24.0 (5.9–98.7)	5.0 (2.7–9.1)
>60 to 70	836	122.5±14.2	53 (8.2)	5.5 (2.2–13.8)	2.0 (1.3–3.1)
>70 to 80	2635	128.6±11.0	83 (3.9)	1.5 (0.9–2.5)	0.9 (0.7–1.3)
>80 to 90	1617	136.8±10.6	56 (4.6)	Reference	Reference
>90 to 100	157	149.1±11.9	8 (7.1)	1.0 (0.4–2.4)	1.7 (0.8–3.6)
>100	18	163.7±19.3	0 (0.0)	–	–

BP indiactes blood pressure; CI, confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; SBP, systolic blood pressure.

and diastolic BPs at baseline and on treatment were associated with greater cardiovascular risk.

In patients treated for hypertension, the 2017 AHA/ACC hypertension guidelines recommended a target of <130/80 mm Hg for patients with ischemic heart disease and for patients with diabetes mellitus.[13] Our results suggest that an ideal BP target for patients with hypertension, ischemic heart disease, and type 2 diabetes mellitus may be somewhat

Table 8. Stroke (Nonfatal) Through 24 Months by BP Category

SBP Group (mm Hg)	Total Patients	DBP (mm Hg), Mean±SD	Incidence Rate, n (%)	Average Follow-up SBP, Adjusted HR (95% CI)	Baseline SBP, Adjusted HR (95% CI)
≤100	49	62.8±5.5	2 (6.1)	64.7 (6.5–648.4)	8.9 (1.7–46.4)
>100 to 110	224	67.8±6.4	2 (1.2)	6.2 (0.9–44.8)	1.4 (0.3–6.6)
>110 to 120	851	72.6±5.7	6 (1.0)	2.3 (0.7–8.3)	0.9 (0.3–2.4)
>120 to 130	1619	76.0±5.8	15 (1.1)	1.6 (0.7–3.6)	0.9 (0.5–2.0)
>130 to 140	1519	79.1±6.2	16 (1.4)	Reference	Reference
>140 to 150	731	81.1±7.7	8 (1.5)	0.5 (0.2–1.4)	0.9 (0.4–2.1)
>150 to 160	276	82.2±8.6	11 (5.9)	0.9 (0.3–3.3)	2.9 (1.3–6.7)
>160	111	85.2±11.2	4 (5.3)	0.3 (0.0–3.0)	2.5 (0.7–8.4)
DBP Group (mm Hg)	**Total Patients**	**SBP (mm Hg), Mean±SD**	**Incidence Rate, n (%)**	**Average Follow-up DBP, Adjusted HR (95% CI)**	**Baseline DBP, Adjusted HR (95% CI)**
≤60	117	118.2±16.0	1 (1.0)	16.1 (0.7–368.8)	1.0 (0.1–8.2)
>60 to 70	836	122.5±14.2	10 (1.6)	6.8 (1.2–37.7)	1.2 (0.5–2.9)
>70 to 80	2635	128.6±11.0	24 (1.2)	1.7 (0.7–4.2)	0.7 (0.4–1.3)
>80 to 90	1617	136.8±10.6	23 (2.0)	Reference	Reference
>90 to 100	157	149.1±11.9	5 (3.8)	0.8 (0.2–2.8)	2.0 (0.7–5.5)
>100	18	163.7±19.3	1 (5.6)	0.3 (0.0–4.7)	2.6 (0.3–20.8)

BP indicates blood pressure; CI, confidence interval; DBP, diastolic blood pressure; HR, hazard ratio; SBP, systolic blood pressure.

Table 9. Patient Characteristics and BPs by Nonfatal MACE

Patient Characteristics	No Nonfatal MACE (n=4971)	Nonfatal MACE (n=409)	*P* Value
Age, y	60.7±10.0	62.7±9.4	<0.001
Male sex	3383 (68.1)	268 (65.5)	0.292
Heart rate, bpm	71.3±10.7	71.6±11.4	0.605
Current smoker	682 (13.7)	52 (12.7)	0.569
BMI, kg/m^2	29.4±5.6	30.1±5.9	0.017
eGFR, mL/min per 1.73 m^2	71.5±21.2	64.5±22.8	<0.001
MI	4358 (87.7)	376 (90.1)	0.011
Heart failure	1360 (27.4)	141 (34.5)	0.002
PAD	437 (8.8)	77 (18.8)	<0.001
Stroke	129 (2.6)	16 (3.9)	0.114
Hypertension	4094 (82.4)	375 (91.7)	<0.001
Duration of diabetes mellitus, y	9.0±8.1	11.5±9.0	<0.001
Insulin	1437 (28.9)	168 (41.1)	<0.001
Aspirin	4500 (90.5)	381 (93.2)	0.078
Statins	4493 (90.4)	373 (91.2)	0.590
β-Blockers	4074 (82.0)	337 (82.4)	0.824
RAS blocking agents	4069 (81.9)	342 (83.6)	0.372
Average clinician BP, mm Hg			
SBP	130.3±12.9	133.7±17.1	<0.001
DBP	77.1±7.5	76.2±9.4	0.045
Baseline BP (mm Hg)			
SBP	128.6±16.5	133.0±17.4	<0.001
DBP	76.5±9.6	75.5±10.6	0.081
Final BP (mm Hg)			
SBP	130.4±14.9	134.0±19.8	0.001
DBP	76.9±9.1	76.6±11.1	0.647
Number of BP measurements	7.2±2.8	3.3±1.8*	<0.001
Follow-up, mo, median (IQR)	19.4 (11.5–25.9)	20.9 (14.0–27.2)	

Data are shown as mean±SD or n (%) except as noted. BMI indicates body mass index; BP, blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MACE, major adverse cardiac events; MI, myocardial infarction; PAD, peripheral artery disease; RAS, renin–angiotensin system; SBP, systolic blood pressure.
*Measurements were censored after an event occurred.

higher than this recommendation. Furthermore, there is substantially increased cardiovascular hazard if the clinician-measured BP is <120/70 mm Hg, an issue that has not been comprehensively addressed in recent guidelines.[13–17] In 2015, SPRINT[4] demonstrated that achieving a systolic BP of <120 mm Hg in patients with increased cardiovascular risk was associated with a reduction in BP-related adverse outcomes, particularly hospitalization for heart failure and death due to cardiovascular causes. Recent post hoc and secondary analyses of SPRINT have shown that patients who had low baseline cardiovascular risk had less benefit and more adverse renal events in the intensively treated group than in the standard group.[21] Furthermore, those patients in the lowest quintile of diastolic BP at baseline (61 mm Hg) had higher rates of cardiovascular events, but there was still marginal benefit from intensive lowering of systolic BP in this group with low diastolic BP.[22] The level of BP in SPRINT was based on digital measurements by a device not requiring the attendance of a physician or nurse, a measurement technique now recommended in the 2017 ACC/AHA BP guidelines.[13] These types of measurements, which avoid talking and the anxiety provoked by a clinician's presence, are estimated to be several millimeters of mercury lower than systolic BPs obtained by manual measurement by a physician or nurse.[23,24] Patients in EXAMINE had standard measurements of BP taken by clinicians, as is typically done in practice; therefore, it is likely that the results relating BP

Table 10. Patient Characteristics and BPs by Hospitalization for Heart Failure

Patient Characteristics	No Heart Failure (n=5189)	Heart Failure Hospitalization (n=191)	*P* Value
Age, y	60.8±9.9	63.6±10.0	<0.001
Male sex	3536 (68.1)	115 (60.2)	0.021
Heart rate, bpm	71.2±10.6	76.0±13.1	<0.001
Current smoker	713 (13.7)	21 (11.0)	0.278
BMI, kg/m^2	29.4±5.5	30.2±7.6	0.154
eGFR, mL/min per 1.73 m^2	71.5±21.2	56.2±22.4	<0.001
MI	4551 (87.7)	183 (95.8)	<0.001
Heart failure	1377 (26.5)	124 (64.9)	<0.001
PAD	420 (9.1)	44 (23.0)	<0.001
Stroke	138 (2.7)	7 (3.7)	0.399
Hypertension	4300 (82.9)	169 (88.5)	0.042
Duration of diabetes mellitus, y	9.0±8.0	13.4±11.0	<0.001
Insulin	1514 (29.2)	91 (47.6)	<0.001
Aspirin	4704 (90.7)	174 (91.1)	0.856
Statins	4700 (90.6)	166 (86.9)	0.091
β-Blockers	4255 (82.0)	156 (81.7)	0.909
RAS blocking agents	4256 (82.0)	155 (81.2)	00.759
Average clinician BP, mm Hg			
SBP	130.7±13.1	128.6±17.4	0.110
DBP	77.2±7.5	74.8±10.1	0.001
Baseline BP, mm Hg			
SBP	129.1±16.5	126.1±19.1	0.036
DBP	76.5±9.6	73.0±10.8	<0.001
Final BP, mm Hg			
SBP	130.7±15.2	129.8±19.1	0.587
DBP	76.9±9.1	74.8±11.6	0.028
Number of BP measurements	7.1±2.9	3.0±1.9*	<0.001
Follow-up, mo, median (IQR)	19.5 (11.8–26.0)	21.2 (12.9–26.1)	0.262

Data are shown as mean±SD or n (%) except as noted. BMI indicates body mass index; BP, blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MACE, major adverse cardiac events; MI, myocardial infarction; PAD, peripheral artery disease; RAS, renin–angiotensin system; SBP, systolic blood pressure.
*Measurements were censored after an event occurred.

levels to cardiovascular outcomes from SPRINT versus those found in EXAMINE are not comparable based on the variance in BP measurement methodology as well as differences in patient populations.

Analyses from other preventive cardiology clinical trials support our findings. The ACCOMPLISH trial, which studied patients with hypertension and increased cardiovascular risk, found that, compared with a systolic BP ≥140 mm Hg, achieving <140 mm Hg produced significant cardiovascular outcomes benefits—but there was no further benefit at lower systolic BP levels.[10] As in EXAMINE, however, systolic BP was not intentionally treated to lower goals as a comparison. For patients with recent ACSs, the PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy) trial reported that achieved BPs of 136/85 mm Hg were associated with the lowest secondary cardiovascular event rates in a population of primarily nondiabetic patients.[11]

A linear relationship between levels of BP and cardiovascular outcomes has been observed in the general hypertensive population, particularly for stroke; however, in patients with coronary artery disease, the relationship between BP and cardiovascular outcomes often shows a J- or a U-shaped curve, with higher cardiovascular event rates at lower levels of BP.[25] Patients with ischemic heart disease who develop

Table 11. Patient Characteristics and BPs by Cardiovascular Death

Patient Characteristics	Alive (n=5160)	Cardiovascular Death (n=220)	*P* Value
Age, y	60.7±9.9	65.8±9.9	<0.001
Male sex	3520 (68.2)	131 (59.5)	0.007
Heart rate, bpm	71.3±10.7	73.0±12.5	0.046
Current smoker	711 (13.8)	23 (10.5)	0.159
BMI, kg/m^2	29.5±5.6	28.6±6.4	0.154
eGFR, mL/min per 1.73 m^2	71.5±21.1	57.4±23.2	<0.001
MI	4523 (87.7)	211 (95.9)	<0.001
Heart failure	1394 (27.0)	107 (48.6)	<0.001
PAD	482 (9.3)	32 (23.0)	<0.001
Stroke	139 (2.7)	6 (2.7)	0.976
Hypertension	4268 (82.7)	201 (91.4)	<0.001
Duration of diabetes mellitus, y	9.0±8.1	11.8±9.0	<0.001
Insulin	1532 (29.7)	73 (33.2)	0.268
Aspirin	4696 (91.0)	185 (84.1)	<0.001
Statins	4675 (90.6)	191 (86.8)	0.062
β-Blockers	4250 (82.4)	161 (73.2)	<0.001
RAS blocking agents	4230 (82.0)	181 (82.3)	0.911
Average clinician BP, mm Hg			
SBP	130.6±13.1	131.0±17.0	0.741
DBP	77.2±7.5	75.2±9.5	0.003
Baseline BP, mm Hg			
SBP	128.9±16.6	130.7±18.0	0.125
DBP	76.5±9.6	75.6±10.9	0.265
Final BP, mm Hg			
SBP	130.7±15.2	129.9±18.0	0.585
DBP	76.9±9.2	75.4±11.6	0.062
BP measurements, n	7.1±2.9	3.1±1.8*	<0.001
Follow-up, mo, median (IQR)	20.1 (12.5–26.3)	7.3 (3.2–13.4)	<0.001

Data are shown as mean±SD or n (%) except as noted. BMI indicates body mass index; BP, blood pressure; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MACE, major adverse cardiac events; MI, myocardial infarction; PAD, peripheral artery disease; RAS, renin–angiotensin system; SBP, systolic blood pressure.
*Measurements were censored after an event occurred.

reduced coronary perfusion pressure and have altered autoregulatory capacity due to endothelial dysfunction and oxidative stress may be susceptible to ischemic events in a condition of low BP, particularly during diastole.[26] It is also possible that a J-curve relationship occurs because of preexisting disease, and reverse causality is playing a role in the relationship. In EXAMINE, the former etiology seems more plausible because the relationship of baseline BP and cardiovascular outcomes was weak, whereas the relationship with longer term postrandomization average BP and cardiovascular outcomes was more robust—a finding also seen in PROVE-IT[11] and in a secondary analysis of TNT (Treating to New Targets Trial)[27]. Furthermore, BP values late in the trial period differed by only 4/0 mm Hg in those patients with nonfatal MI, stroke, or heart failure hospitalization, suggesting that reverse causality was improbable for the nonfatal events. These new results from EXAMINE extend our knowledge in patients with type 2 diabetes mellitus and a recent coronary event, suggesting the hypothesis that BP should not be lowered excessively under 130/80 mm Hg. Ultimately, this hypothesis should be tested in a randomized controlled trial testing different BP targets.

A limitation of our study is that although BP was measured by clinicians using recommended AHA methods, the BP

devices were not standardized across centers. In addition, although recommendations were made to manage all cardiovascular risk factors according to standard of care during the conduct of the EXAMINE trial, lower BP levels were not necessarily achieved by purposefully intensifying therapy to achieve a BP goal <140/90 mm Hg. In addition, the numbers of patients and events in the highest category of systolic BP (>160 mm Hg) were too small to provide meaningful relationships compared with the reference group. Because this post hoc analysis is derived from a population with a recent ACS and type 2 diabetes mellitus, the results cannot be extrapolated to other populations with chronic hypertension. Our study is strengthened by the fact that we had a well-characterized sample with substantial follow-up, a high cardiovascular event rate, and blinded adjudications of all cardiovascular events and deaths. In addition, because BP values did not drop in those patients with events toward the latter part of the study and their median duration in the trial was similar to those who did not have an event, the association between achieved BPs and cardiovascular outcomes seen in EXAMINE did not appear likely to be due to reverse causality.

The EXAMINE study, which was composed of a patient population with type 2 diabetes mellitus and a recent ACS, demonstrated that BPs <130/80 mm Hg were associated with an increased risk of secondary cardiovascular events, including mortality. These data suggest that excessively intensive control of BP in patients with type 2 diabetes mellitus and ischemic heart disease may be harmful and create a hypothesis that should be tested in a randomized controlled trial.

Acknowledgments

All authors take full responsibility for the work as a whole, including the study design and the decision to submit and publish the article. White and Jalil wrote the initial and subsequent drafts of the article after reviews and edits from coauthors. Liu performed statistical analyses and reviewed the article. Cushman, Zannad, Mehta, Bakris, Heller, Bergenstal, and Cannon reviewed/edited the article.

Sources of Funding

This work was supported by Takeda Development Center, North America.

Disclosures

White is chair of the EXAMINE steering committee and has received personal fees from Takeda Development Center, Deerfield, IL; Zannad is a member of the EXAMINE steering committee and has received personal fees from Takeda Development Center, Deerfield, IL, Mehta is a member of the EXAMINE steering committee has received personal fees from Takeda Development Center, Deerfield IL, Liu, is an employee of Baim Clinical Research Group, Boston, MA, Bakris is a member of the EXAMINE steering committee and has received personal fees from Takeda Development Center, Deerfield, IL; Cushman is a member of the EXAMINE steering committee and has no disclosures; Heller is a member of the EXAMINE steering committee and has received personal fees from Takeda Development Center, Deerfield, IL; Bergenstal is a member of the EXAMINE steering committee and has received personal fees from Takeda Development Center, Deerfield, IL; and Cannon is an employee of the Baim Clinical Research Institute, Boston, MA.

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