Original Paper

Association of a History of Systemic Hypertension With Mortality, Thrombotic, and Bleeding Complications Following Non–ST-Segment Elevation Acute Coronary Syndrome

Raphaelle Dumaine, MD; C. Michael Gibson, MS, MD; Sabina A. Murphy, MPH; Matthew Southard, BS; Hung Q. Ly, MD; Carolyn H. McCabe, BS; Robert P. Giugliano, MD; Christopher P. Cannon, MD; Elliott M. Antman, MD; Eugene Braunwald, MD

Chronic hypertension is a well established risk factor for the development of cardiovascular disease; however, its prognostic significance after a non–ST-segment elevation acute coronary syndrome remains to be established. Data from 15,414 patients included in six randomized Thrombolysis in Myocardial Infarction (TIMI) trials (TIMI 3B, TIMI 11A, TIMI 11B, TIMI 12, the Orbofiban in Patients With Unstable Coronary Syndromes [OPUS]-TIMI 16, and the Treat Angina With Aggrastat and Determine Cost of Therapy With an Invasive or Conservative Strategy [TACTICS]-TIMI 18) were analyzed. A history of hypertension was present in 10,998 (71.35%) patients; comorbidities and higher TIMI risk scores were more likely in these patients. However, positive troponin and ST-segment deviations were less frequent among hypertensive patients. After multivariate analysis, the history of hypertension was associated with more adverse outcomes, specifically the composite end point of death/myocardial infarction at 30 days and 1 year (odds ratio [OR] 1.54, 95% confidence interval [CI] 1.31–1.81; p<0.001 at 1 year) than in patients without this history. An independent relationship was also observed with mortality (OR 1.70, 95% CI 1.34–2.16; p<0.001 at 1 year), myocardial infarction (OR 1.50, 95% CI 1.23–1.82; p<0.001 at 1 year), recurrent ischemia (OR 1.24, 95% CI 1.11–1.38; p<0.001 at 1 year), and major bleeding (OR 1.45, 95% CI 1.03–2.06; p=0.036 at 30 days). It was concluded that chronic hypertension remains an independent marker for major short- and long-term cardiac adverse outcomes after non–ST-segment elevation acute coronary syndrome. (J Clin Hypertens. 2006;8:315–322) ©2006 Le Jacq Ltd.

From the Thrombolysis in Myocardial Infarction (TIMI) Study Group, Cardiovascular Division, Department of Medicine, Brigham & Women's Hospital, and Harvard Medical School, Boston, MA
Address for correspondence:
Eugene Braunwald, MD, Chairman, TIMI Study Group, 350 Longwood Avenue, First Floor, Boston, MA 02115
E-mail: ebraunwald@partners.org
Manuscript received December 5, 2005; revised March 8, 2006; accepted March 22, 2006

www.lejacq.com ID: 5384

Chronic hypertension (HTN) is well established as a risk factor for the development of atherosclerosis,[1] and an increased incidence of peripheral vascular disease,[2] cerebrovascular disease,[3] renal disease,[4] and coronary artery disease.[5] Despite the extensive epidemiologic data regarding the prevalence of HTN and its sequelae in the general population, its relationship to prognosis among patients with a non–ST-segment elevation (NSTE) acute coronary syndrome (ACS) is not well established; data are conflicting. In a recent pooled analysis from randomized NSTE-ACS clinical trials,[6] HTN was

an independent correlate of mortality, while another study of the ACS failed to identify a difference in long-term outcomes when comparing hypertensive and nonhypertensive patients.[7] The purpose of the present analysis was to assess the importance of HTN as a prognostic factor in a large population of patients presenting with NSTE-ACS.

METHODS

Clinical data were drawn from six NSTE-ACS Thrombolysis in Myocardial Infarction (TIMI) studies (TIMI 3B, TIMI 11A, TIMI 11B, TIMI 12, Orbofiban in Patients With Unstable Coronary Syndromes [OPUS]-TIMI 16, and Treat Angina With Aggrastat and Determine Cost of Therapy With an Invasive or Conservative Strategy [TACTICS]-TIMI 18) and were available among 15,414 patients. The designs of the different trials have been previously published. In brief, TIMI 3B was a randomized trial with a 2 × 2 factorial design comparing recombinant tissue plasminogen activator to placebo and early invasive compared with conservative strategy among NSTE-ACS patients.[8] The TIMI 11A trial[9] was a dose-ranging trial to establish the optimal safety and efficacy for further testing of enoxaparin (a low molecular weight heparin), and the TIMI 11B trial[10] was a randomized trial comparing safety and efficacy of enoxaparin compared with unfractionated heparin among NSTE-ACS patients. The randomized TIMI 12[11] and OPUS-TIMI 16[12] trials evaluated the safety and efficacy of oral glycoprotein IIb/IIIa inhibitors (sibrafiban and orbofiban, respectively) among ACS patients, but only patients presenting with NSTE-ACS were taken into account in the present analysis. Finally, TACTICS-TIMI 18 was a trial comparing outcomes of NSTE-ACS patients randomized to early invasive (cardiac catheterization with percutaneous coronary intervention, if necessary) or medical therapy strategies following the administration of tirofiban, a glycoprotein IIb/IIIa inhibitor.[13] The definition of NSTE-ACS was consistent across trials and included those patients with symptoms of an ACS, including those with symptoms at rest, ST depression, or positive troponin, but excluded patients with ST-segment elevation. Each trial was approved by an institutional review board. All patients gave written informed consent to participate in the trials.

Angiographic Analyses

Angiographic data were available in 540 patients from the TACTICS-TIMI 18 trial. Angiographic outcomes were assessed by a single observer (CMG) blinded to clinical outcomes and treatment strategy assignment. The TIMI flow grade,[14] corrected TIMI frame count,[15–17] and TIMI myocardial perfusion grade[18] were assessed as previously defined.

Clinical Definitions

Patients were defined as hypertensive in all trials by either having a known history of HTN or being treated with antihypertensive medication at the time of the qualifying event. Accordingly, nonhypertensive patients did not have either of these criteria. Creatinine clearance was estimated using the Cockcroft-Gault equation[19] and expressed in mL/min.

End Point Definitions

All-cause mortality was assessed from randomization through 1-year follow-up, if available. The incidence of minor and major bleeding, intracranial hemorrhage, stroke, myocardial infarction (MI), and recurrent ischemia (RI) were assessed as previously defined[20] from randomization through 30 days of follow-up. The TIMI risk score for NSTE-ACS was evaluated as previously reported.[21]

Statistical Analyses

All continuous variables are reported as the mean ± SD. The chi-square test was used for the analysis of categoric variables. Student *t* test was used for the comparison of continuous variables. All tests were two-sided. Adverse event rates at 1-year follow-up were compared using survival analysis techniques including Kaplan-Meier hazard estimates and the log-rank test; p values ≤ 0.05 were considered significant. Multivariable Cox proportional hazard models or logistic regression models were used for the analysis of clinical end points, adjusting for clinical baseline characteristics: gender, age per 10-year increase, ethnicity, smoking status, prior MI, history of HTN, diabetes, percutaneous coronary intervention, diagnosis on admission (NSTE-MI vs. unstable angina), ST-segment deviation, systolic and diastolic blood pressure, heart rate on admission, as well as creatinine clearance per 10-unit increase. All analyses were performed using Stata version 7.0 (StataCorp LP, College Station, TX).

RESULTS

Baseline Characteristics

Baseline characteristics of patients are detailed in Table I. Among the 15,414 patients, 71.3% had a history of HTN. A history of HTN was associated with a higher baseline risk profile on admission. Patients with HTN were more likely to be older,

Table I. Baseline Characteristics

	No Hypertension (n=4416)	Hypertension (n=10,998)	*p* Value
Female	24.4 (1078)	36.2 (3987)	<0.001
Age (yr) (mean ± SD)	58.2±11.7 (4405)	63.5±11.1 (10964)	<0.001
Age >65 yr	30.8 (1357)	49.9 (5468)	<0.001
Ethnicity (% white)	90.7 (4002)	86.8 (9548)	<0.001
Cigarette smoking	45.2 (1990)	24.6 (2663)	<0.001
Prior myocardial infarction (MI)	16.4 (722)	42.4 (4665)	<0.001
History of diabetes	12.2 (516)	26.8 (2817)	<0.001
Hypercholesterolemia	21.4 (919)	41.8 (4336)	<0.001
History of heart failure	1.2 (46)	8.9 (882)	<0.001
Prior percutaneous coronary intervention	7.0 (310)	20.2 (2217)	<0.001
Prior coronary bypass grafting surgery	7.0 (282)	19.0 (1893)	<0.001
Congestive heart failure on admission	4.9 (110)	9.5 (433)	<0.001
Non–ST-segment elevation MI	48.0 (2016)	30.1 (3073)	<0.001
Unstable angina	52.0 (2187)	69.9 (7149)	<0.001
Presence of ST-segment deviation	61.0 (2432)	57.8 (5680)	0.001
Positive troponin on admission	60.6 (335)	42.1 (761)	<0.001
Admission systolic BP (mm Hg) (mean ± SD)	128.5±20.6	134.5±21.6	<0.001
Admission diastolic BP (mm Hg) (mean ± SD)	75.0±12.8	76.0±12.9	<0.001
Admission heart rate (bpm) (mean ± SD)	72.9±13.8	72.8±14.3	0.671
Creatinine clearance (mL/min) (mean ± SD)	102.9±38.7 (3740)	90.3±38.6 (9394)	<0.001
TIMI risk score 0–2	58.8 (2464)	29.2 (2858)	<0.001
TIMI risk score 3–4	37.7 (1582)	57.0 (5580)	
TIMI risk score ≥5	3.5 (147)	13.8 (1345)	
Prior medications at baseline			
Aspirin	38.4 (1686)	70.3 (7716)	<0.001
Lipidemic therapy	9.4 (413)	27.1 (2971)	<0.001
β Blockers*	0 (0)	47.5 (5217)	<0.001
ACE inhibitors*	0 (0)	28.1 (3084)	<0.001
Diuretics*	0 (0)	24.0 (2639)	<0.001

Results are displayed as % (n), except as otherwise indicated. BP=blood pressure; TIMI=Thrombolysis in Myocardial Infarction; *hypertensive patients were defined as either having a known history of hypertension or being treated with antihypertensive medication at the time of the qualifying event. Therefore, by definition, use of β blockers, angiotensin-converting enzyme (ACE) inhibitors, and diuretics was 0% for nonhypertensive patients.

female, of nonwhite ethnicity, and have a higher TIMI risk score and greater prevalence of comorbidities, such as diabetes, hypercholesterolemia, renal insufficiency, history of congestive heart failure, prior MI, prior percutaneous coronary intervention, or prior coronary artery bypass grafting. However, hypertensive patients were less likely to have positive troponin and ST-segment deviation and fewer were current smokers. They were more frequently considered to have unstable angina and, conversely, had NSTE-MI less frequently than nonhypertensive patients. On admission, hypertensive patients, not surprisingly, had higher systolic and diastolic blood pressures and more clinical evidence of heart failure than other patients ($p<0.001$ for all, Table I).

Angiographic Findings

Coronary artery disease was more extensive among patients with HTN: 24.2% had three-vessel disease (as compared with 13.9% nonhypertensive patients), 37.9% had two-vessel disease (vs. 29.2%), and 37.9% had one-vessel disease (vs. 56.9%) (p value for trend <0.001). No difference was observed between the two groups with respect to degree of stenosis of the culprit lesion before percutaneous coronary intervention, corrected TIMI frame count, TIMI flow grade, and TIMI myocardial perfusion grade. In addition, frequency of the presence of a thrombus was not different among the two groups (data not shown).

Outcomes at 30 Days and 1 Year

A history of HTN was associated with a significantly higher incidence of death, MI, and RI, as well as in the composites of these events at 30 days (Table II). In addition, stroke, congestive heart failure, and TIMI major bleeding all occurred more frequently among patients with HTN. When the

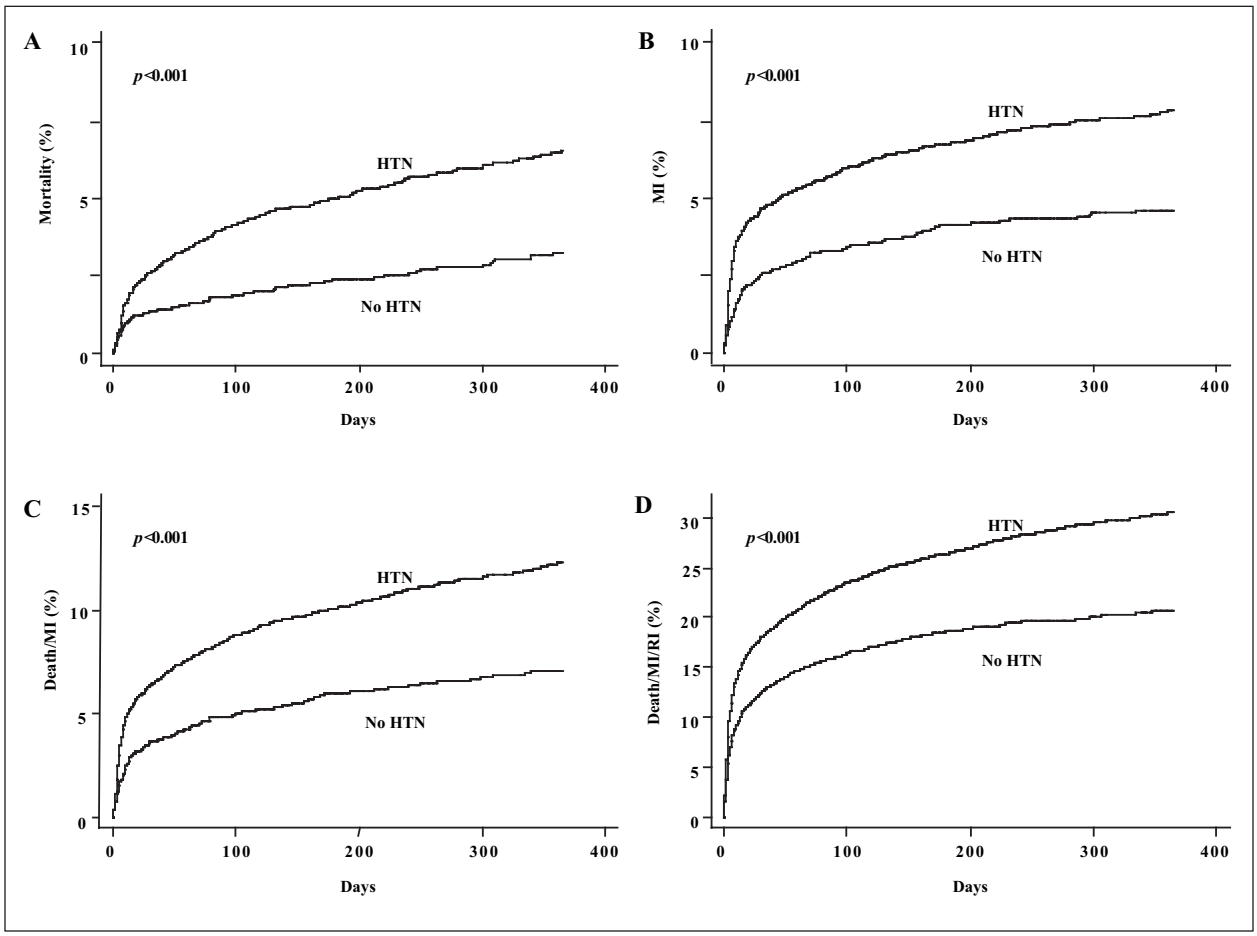

Figure 1. Kaplan-Meier survival estimates of death (A), myocardial infarction (MI) (B), and of the composite end points of death/MI (C) and death/MI/recurrent ischemia (RI) (D) at 1-year follow-up among patients with hypertension (HTN) and without a history of hypertension (no HTN). The p *value is based on the log-rank test.*

Table II. Outcomes at 30 Days by Hypertension Groups

	No Hypertension	Hypertension	Unadjusted OR [95% CI]	*P* Value
Death	1.3 (58)	2.6 (283)	1.98 [1.49–2.64]	<0.001
MI or recurrent MI	2.5 (111)	4.5 (499)	1.84 [1.50–2.27]	<0.001
Recurrent ischemia	9.7 (429)	13.9 (1526)	1.50 [1.34–1.68]	<0.001
Death/MI	3.6 (158)	6.3 (695)	1.82 [1.52–2.17]	<0.001
Death/MI/recurrent ischemia	12.4 (549)	17.8 (1952)	1.52 [1.37–1.68]	<0.001
Stroke	0.4 (17)	0.8 (80)	1.96 [1.16–3.30]	0.011
Congestive heart failure	1.1 (42)	1.8 (178)	1.72 [1.22–2.41]	0.001
TIMI major bleeding	3.2 (55)	4.6 (247)	1.46 [1.08–1.96]	0.013
TIMI minor bleeding	4.5 (94)	5.3 (339)	1.21 [0.95–1.52]	0.117

Results are displayed as % (n). OR=odds ratio; CI=confidence interval; MI=myocardial infarction; TIMI=Thrombolysis in Myocardial Infarction

analysis was stratified based on gender, age, diabetic status, and renal function, HTN remained associated with poorer clinical outcomes (Table III). No significant interaction was observed between HTN and these comorbidities (data not shown).

These differences in clinical outcomes were maintained at 1 year (Figure 1). In univariate analysis at 1 year, HTN was associated with a higher incidence of death, MI, RI, as well as the composites of these events, and congestive heart failure ($p<0.001$ for all).

Multivariate Analyses

After adjustment for differences in baseline clinical characteristics, HTN was among the strongest

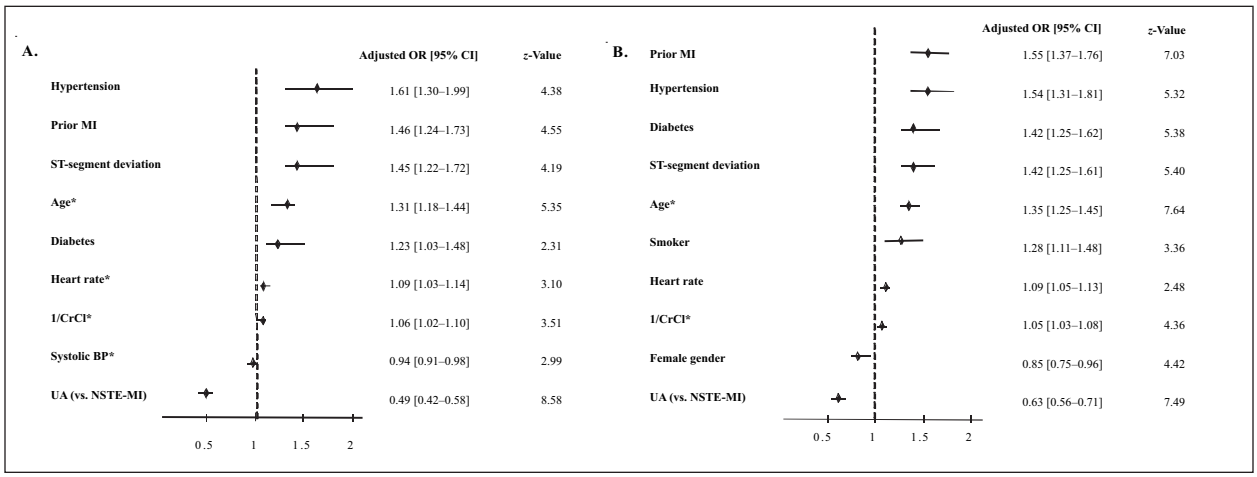

*Figure 2. Significant correlates for death/myocardial infarction (MI) at 30 days (A) and at 1 year (B) after adjustment for baseline characteristics. OR=odds ratio; CI=confidence interval; CrCl=creatinine clearance; BP=blood pressure; NSTE-MI=non–ST-segment elevation myocardial infarction; UA=unstable angina; *per 10-unit increase*

correlates in its association, with the composite end points of death/MI at 30 days (odds ratio 1.61, 95% confidence interval 1.30–1.99; $p<0.001$) and at 1 year (odds ratio 1.54, 95% confidence interval 1.31–1.81; $p<0.001$) (Figure 2). HTN was also independently associated with the end points of death, MI, RI, and their combinations as well as with major bleeding (Table IV).

DISCUSSION

Epidemiologic studies have shown that chronic HTN is the most prevalent traditional coronary risk factor among patients with NSTE-ACS and is present in almost two thirds of patients with this condition.[22] The association between a history of HTN and the development of coronary heart disease is well established in the general population;[5] however, the association of a history of HTN with clinical outcomes in the setting of an ACS is not well defined. The present analysis of more than 15,000 patients demonstrates that chronic HTN is an independent risk factor for major adverse cardiac events in the setting of, and following, an episode of NSTE-ACS.

Prior analyses have yielded conflicting results. A recent hospital-based study[7] of 979 patients with ACS did not find any difference of in-hospital or 6-month mortality among hypertensive as compared with nonhypertensive patients. Among patients drawn from the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial,[23] a history of HTN was associated with a higher number of deaths at 30 days in univariate but not in multivariate analysis (odds ratio 1.25, 95% confidence interval 0.97–1.62). However, when data were pooled from other studies, i.e., the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO IIb), Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON A and B), and PURSUIT trials, chronic HTN was independently associated with long-term mortality in a multivariate analysis (odds ratio 1.23, 95% confidence interval 1.05–1.44).[6]

The results of the present analysis are consistent with and extend this latter observation by demonstrating additional associations between chronic HTN and MI, RI, and major bleeding. The increased risk of adverse outcome was consistent across most demographic subgroups. The present analysis also demonstrates that despite the significant differences in baseline characteristics between the hypertensive and nonhypertensive groups, the prognostic importance of chronic HTN is strong and independent of age, renal function, smoking status, and prior MI, as well as comorbidities frequently associated with HTN, such as diabetes and hypercholesterolemia. Furthermore, it demonstrates the long-term consequence of HTN as a chronic process; the association between HTN and adverse outcomes appears to be independent of the level of blood pressure on admission.

Previous data have not uniformly demonstrated a similar association between chronic HTN and clinical outcomes. This may be due to a lack of statistical power in smaller studies or variability in the definition chosen for HTN.

In the present study, angiographic coronary artery disease, assessed in a subset of patients was, as might be expected, more extensive among hypertensive patients. This might account at least in

Table III. Main Outcomes at 30 Days by Hypertension Subgroups

	Women (n=5061)		Men (n=10,334)		Age ≥75 yr (n=2278)		Age <75 yr (n=13,068)		Diabetes (n=3332)		No Diabetes (n=11,393)		CrCl <60 mL/min (n=2393)		CrCl ≥60 mL/min (n=10,741)	
	HTN –	HTN +	HTN –	HTN +	HTN –	HTN +	HTN –	HTN +	HTN –	HTN +	HTN –	HTN +	HTN –	HTN +	HTN –	HTN +
Death	1.9	2.9*	1.1	2.4	3.6	6.3	1.1	1.8	1.4	3.2	1.3	2.4	2.0	6.0	1.1	1.8
MI/recurrent MI	2.2	4.6	2.6	4.5	4.1	6.5*	2.3	4.2	2.5	5.4	2.4	4.1	4.2	6.7*	2.3	3.7
Death/MI	3.8	6.6	3.5	6.2	7.2	11.0	3.2	5.4	3.5	7.6	3.5	5.7	5.6	11.0	3.2	5.0
Major bleeding	4.1	5.1*	2.9	4.4	4.8	7.4*	3.0	4.0*	3.4	4.9*	3.0	4.4	5.5	7.0*	2.2	3.3

CrCl=creatinine clearance; HTN–=nonhypertensive; HTN+=hypertensive; MI=myocardial infarction. Results are displayed as percentages. All *p* values for comparisons between hypertensive and nonhypertensive subgroups are ≤0.05 unless indicated by *.

Table IV. Effects of Hypertension on Main Outcomes at 30 Days and 1 Year

	At 30 Days				At 1 year			
Outcomes	No. Events/Observations	*Z* Value	Adjusted* OR [95% CI]	*P* Value	No. Events/Observations	*Z* Value	Adjusted* HR [95% CI]	*P* Value
Death/myocardial infarction	675/12,128	4.38	1.61 [1.30–1.99]	<0.001	1,160/12,016	5.32	1.54 [1.31–1.81]	<0.001
Death/myocardial infarction/ recurrent ischemia	1,895/12,128	4.18	1.30 [1.15–1.47]	<0.001	3,032/12,038	5.43	1.29 [1.18–1.42]	<0.001
Death	275/12,128	3.07	1.72 [1.21–2.42]	0.002	574/11,998	4.35	1.70 [1.34–2.16]	<0.001
Myocardial infarction	479 /12,128	3.75	1.61 [1.25–2.06]	<0.001	742/11,944	4.02	1.50 [1.23–1.82]	<0.001
Recurrent ischemia	1,413/12,046	3.37	1.26 [1.10–1.44]	0.001	2,278/11,975	3.94	1.24 [1.11–1.38]	<0.001
Major bleeding	237/5971	2.1	1.45 [1.03–2.06]	0.036	–	–	–	–

OR=odds ratio; CI=confidence interval; *parameters adjusted for included gender, age per 10-year increase, ethnicity, smoking status, prior myocardial infarction, history of hypertension, diabetes, percutaneous coronary intervention, diagnosis on admission (non–ST-segment elevation myocardial infarction vs. unstable angina), ST-segment deviation, systolic and diastolic blood pressure, heart rate on admission, as well as creatinine clearance per 10-unit increase

part for the higher incidence of adverse outcomes among hypertensive patients. Other pathophysiologic mechanisms may play a role. These include the complications of HTN-induced left ventricular hypertrophy, which may increase the risk of arrhythmias, impaired coronary flow reserve, and impaired myocardial perfusion.[24] Hemorheologic abnormalities, such as hyperviscosity, endothelial dysfunction, and a prothrombotic state have also been associated with HTN.[24] It has been demonstrated that vascular inflammation[25] as well as oxidative stress[26–28] are more prevalent in HTN.

These findings underscore the ongoing risk of adverse outcomes through 1 year among patients with chronic HTN following hospitalization for NSTE-ACS. Aggressive application of preventive management strategies may reduce this risk.

LIMITATIONS

The limitations of the present study are those inherent to randomized clinical trials in which eligibility of patients is restricted. The baseline blood pressure was within the range specified for each trial, and patients with more severe HTN were excluded. However, had they been included, it is expected that the risk for adverse outcome with HTN would have been even higher. Despite multivariate adjustments, residual confounding remains possible. While it is unlikely to be of sufficient magnitude to account for the presence of an independent association, it may have impacted the magnitude of the observed associations.

CONCLUSIONS

Among patients with NSTE-ACS, a history of HTN is strongly and independently associated with short-term (30 days) and intermediate-term (1 year) adverse outcomes, including death, MI, and RI.

Disclosures: The trials used in this analysis were supported in part by a grant from the National Heart, Blood, and Lung Institute (TIMI 3B); Aventis Pharma, Antony, France (TIMI 11 A and B); Genentech, Inc., South San Francisco, CA (TIMI 12); GD Searle, Skokie, IL (OPUS-TIMI 16); and Merck & Co., Blue Bell, PA (TACTICS-TIMI 18). The preparation, review, and approval of the manuscript were independent of the sponsors; there is no conflict of interest to disclose.

REFERENCES

1 Dzau VJ. Atherosclerosis and hypertension: mechanisms and interrelationships. *J Cardiovasc Pharmacol.* 1990;15(suppl 5):S59–S64.
2 Murabito JM, D'Agostino RB, Silbershatz H, et al. Intermittent claudication. A risk profile from The Framingham Heart Study. *Circulation.* 1997;96:44–49.
3 Lewington S, Clarke R, Qizilbash N, et al. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet.* 2002;360:1903–1913.
4 Adamczak M, Zeier M, Dikow R, et al. Kidney and hypertension. *Kidney Int Suppl.* 2002;80:62–67.
5 Levy D, Wilson PW, Anderson KM, et al. Stratifying the patient at risk from coronary disease: new insights from the Framingham Heart Study. *Am Heart J.* 1990;119(3 pt 2):712–717 [discussion 717].
6 Khot UN, Jia G, Moliterno DJ, et al. Prognostic importance of physical examination for heart failure in non-ST-elevation acute coronary syndromes: the enduring value of Killip classification. *JAMA.* 2003;290:2174–2181.
7 Majahalme SK, Smith DE, Cooper JV, et al. Comparison of patients with acute coronary syndrome with and without systemic hypertension. *Am J Cardiol.* 2003;92:258–263.
8 Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. Thrombolysis in Myocardial Ischemia. *Circulation.* 1994;89:1545–1556.
9 Dose-ranging trial of enoxaparin for unstable angina: results of TIMI 11A. The Thrombolysis in Myocardial Infarction (TIMI) 11A Trial Investigators. *J Am Coll Cardiol.* 1997;29:1474–1482.
10 Antman EM, McCabe CH, Gurfinkel EP, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) 11B trial. *Circulation.* 1999;100:1593–1601.
11 Cannon CP, McCabe CH, Borzak S, et al. Randomized trial of an oral platelet glycoprotein IIb/IIIa antagonist, sibrafiban, in patients after an acute coronary syndrome: results of the TIMI 12 trial. Thrombolysis in Myocardial Infarction. *Circulation.* 1998;97:340–349.
12 Cannon CP, McCabe CH, Wilcox RG, et al. Oral glycoprotein IIb/IIIa inhibition with orbofiban in patients with unstable coronary syndromes (OPUS-TIMI 16) trial. *Circulation.* 2000;102:149–156.
13 Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med.* 2001;344:1879–1887.
14 The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. TIMI Study Group. *N Engl J Med.* 1985;312:932–936.
15 Gibson CM, Cannon CP, Daley WL, et al. TIMI frame count: a quantitative method of assessing coronary artery flow. *Circulation.* 1996;93:879–888.
16 Gibson CM, Murphy SA, Rizzo MJ, et al. Relationship between TIMI frame count and clinical outcomes after thrombolytic administration. Thrombolysis In Myocardial Infarction (TIMI) Study Group. *Circulation.* 1999;99:1945–1950.
17 French JK, Ellis CJ, Webber BJ, et al. Abnormal coronary flow in infarct arteries 1 year after myocardial infarction is predicted at 4 weeks by corrected Thrombolysis in Myocardial Infarction (TIMI) frame count and stenosis severity. *Am J Cardiol.* 1998;81:665–671.
18 Gibson CM, Cannon CP, Murphy SA, et al. Relationship of TIMI myocardial perfusion grade to mortality after administration of thrombolytic drugs. *Circulation.* 2000;101:125–130.
19 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16:31–41.
20 Cannon CP, Battler A, Brindis RG, et al. American College of Cardiology key data elements and definitions for measuring the clinical management and outcomes of patients with acute coronary syndromes. A report of the American College of Cardiology Task Force on Clinical Data Standards (Acute Coronary Syndromes Writing Committee). *J Am Coll Cardiol.* 2001;38:2114–2130.
21 Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA.* 2000;284:835–842.

22 Hasdai D, Behar S, Wallentin L, et al. A prospective survey of the characteristics, treatments and outcomes of patients with acute coronary syndromes in Europe and the Mediterranean basin; the Euro Heart Survey of Acute Coronary Syndromes (Euro Heart Survey ACS). *Eur Heart J*. 2002;23:1190–1201.

23 Boersma E, Pieper KS, Steyerberg EW, et al. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. *Circulation*. 2000;101:2557–2567.

24 Lip GY, Felmeden DC, Li-Saw-Hee FL, et al. Hypertensive heart disease. A complex syndrome or a hypertensive 'cardiomyopathy'? *Eur Heart J*. 2000;21:1653–1665.

25 Sesso HD, Buring JE, Rifai N, et al. C-reactive protein and the risk of developing hypertension. *JAMA*. 2003;290:2945–2951.

26 Parik T, Allikmets K, Teesalu R, et al. Oxidative stress and hyperinsulinaemia in essential hypertension: different facets of increased risk. *J Hypertens*. 1996;14:407–410.

27 Russo C, Olivieri O, Girelli D, et al. Anti-oxidant status and lipid peroxidation in patients with essential hypertension. *J Hypertens*. 1998;16:1267–1271.

28 Redon J, Oliva MR, Tormos C, et al. Antioxidant activities and oxidative stress byproducts in human hypertension. *Hypertension*. 2003;41:1096–1101.