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Relation between systolic blood pressure and in-hospital mortality in acute coronary syndromes

Edina Cenko[1], Beatrice Ricci[1], Zorana Vasiljevic[2] , Sasko Kedev[3], Božidarka Knežević[4], Dijana Trninic[5], Irfan Daullxhiu[6], Olivija Gustiene[7], Davor Miličić[8], Olivia Manfrini MD[1], Maria Dorobantu[9,10], Raffaele Bugiardini*[,1]

[1] Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna, Bologna, Italy
[2] Clinical Center of Serbia, University of Belgrade, Belgrade, Serbia
[3] University Clinic of Cardiology, University "Ss. Cyril and Methodius", Skopje, Macedonia
[4] Clinical Center of Montenegro, Center of Cardiology, Podgorica, Montenegro
[5] Clinical Center of Banja Luka, Banja Luka, Republika Srpska, Bosnia and Herzegovina
[6] Department of Cardiology, University Clinical Centre of Kosovo, Prishtina, Kosovo
[7] Department of Cardiology, Lithuanian University of Health Sciences, Kaunas, Lithuania.
[8] Department for Cardiovascular Diseases, University Hospital Center Zagreb, University of Zagreb, Zagreb, Croatia
[9] Cardiology Department, Clinical Emergency Hospital Bucharest, Bucharest, Romania
[10] University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania

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Abstract

Hypertension is a well-established risk factor for coronary artery disease. Nonetheless the relation between blood pressure and prognosis in acute coronary syndrome (ACS) is still matter of debate. This is a cohort study of 12124 patients admitted with a diagnosis of ACS from the International Survey of Acute Coronary Syndromes in Transitional Countries (ISACS-TC, ClinicalTrials.gov NCT01218776) registry from January 2010-September 2014. Systolic blood pressure (SBP) values were categorized in five categories by 20-mmHg increments. Cox proportional hazards regression model was adjusted to clinically and therapeutic relevant covariates, and TIMI Risk Index (TRI) score. The analysis was performed in the entire cohort of ACS and then separately for ST-segment elevation myocardial infarction (STEMI) and non-ST elevation ACS (NSTE-ACS) cohorts respectively. The outcome endpoint was in-hospital mortality. The majority of patients (47.4%) had SBP values within the range ≥140 to <160 mmHg. Patients with SBP<100 mmHg had the highest rates of in-hospital mortality (43.6%) and higher mean TRI score (47.3) as compared with the rest of SBP categories. After adjustments, a 20-mmHg increase in baseline SBP was significantly associated with approximately 30% reduction of in-hospital mortality (HR: 0.66; 95%CI: 0.61–0.72). In the entire study cohort, the adjusted risk of in-hospital mortality was lower within the range of SBP≥140 to <160 mmHg (HR: 0.49; 95%CI: 0.40– 0.59). Similar results were observed in the STEMI cohort. In NSTE-ACS patients, the adjusted risk of in-hospital mortality was lower in either patients with SBP≥140 to <160 mmHg (HR: 0.52; 95%CI: 0.38– 0.72) or SBP≥160 mmHg (HR: 0.54; 95%CI: 0.30–0.97). Moderately high SBP on presentation was independently associated with reduced in-hospital mortality in ACS. The powerful prognostic value of high SBP was even greater in NSTE-ACS.

Keywords: Acute Coronary Syndrome; Systolic Blood Pressure, Mortality.

* Correspondence to: Raffaele Bugiardini, MD, FAHA, FACC, FESC. Department of Experimental, Diagnostic and Specialty Medicine, University of Bologna. Via Massarenti 9 (Padiglione 11), Bologna, 40138, Italy. Telephone and fax number: +39051347290, e-mail: raffaele.bugiardini@unibo.it

Introduction

Several clinical trials and registry studies have established that there is an inverse relationship between systolic blood pressure (SBP) at admission and in-hospital mortality among patients with ST-segment elevation myocardial infarction (STEMI) [1-3]. Accordingly, clinical tools, such as the risk scores incorporate SBP [4-7]. There are, however, few data on the relationship between SBP and non-ST elevation acute coronary syndromes (NSTE-ACS) [7,8].

The American College of Cardiology/American Heart Association and the European Society of Cardiology consensus guidelines fully recognized that the clinician planning therapy for an individual patient must first establish an accurate clinical profile of the patient in terms of symptoms, functional disability, quality of life and risk for subsequent cardiac events [9–13].

We, therefore, tested the prognostic value of SBP in NSTE-ACS, by analyzing retrospectively a large sample of patients with NSTE-ACS from a prospectively designed multihospital database in South East Europe. Comparison was made with STEMI and the overall population of ACS.

Materials and methods

Patient inclusion criteria

This is a cohort study of 12574 patients admitted with a diagnosis of ACS from 58 hospitals reporting data to the International Survey of Acute Coronary Syndromes in Transitional Countries (ISACS-TC, ClinicalTrials.gov NCT01218776) registry from 01 January 2010 to 30 September 2014. Details of the ISACS-TC registry have been previously published [14, 15]. Patients were included in the ISACS-TC registry if they fulfilled the following criteria: age 18 years old or over, symptoms of acute cardiac ischemia, and documented evidence of persistent ST-segment deviation (ST – segment elevation or non-ST – segment elevation) or new left bundle branch block on serial electrocardiograms and elevated biomarkers of myocardial necrosis. Unstable angina was defined as non-ST segment elevation on serial electrocardiograms but normal biomarkers of myocardial necrosis. Patients with missing data on admission SBP measurements were excluded from the study, leaving a final study population of 12124 patients (Figure 1). The study was approved by the local research ethics committee from each hospital.

Data collection, measures and outcomes

The enrolled hospitals periodically uploaded their data to the central server of the ISACS-TC. Data on patient demographics, cardiovascular risk factors, clinical history, heart rate (HR), SBP on admission, Killip Class, electrocardiographic features, cardiac biomarkers, laboratory results, evidence based therapies, invasive procedures performed during hospitalization, and in-hospital mortality, were collected by the designated physician. To analyze the predictive risk of death as a potential confounder, a simple triage risk stratification score- the Thrombolysis In Myocardial Infarction (TIMI) Risk Index (TRI) score- was calculated for each patient [5, 16]. The TRI includes age, presentation HR and presentation SBP and is calculated as (HR × [age/10]^2)/SBP) [5]. The outcome endpoint was in-hospital mortality.

Statistical analysis

Baseline SBP values were categorized in five categories by 20 mmHg increments for evaluating association with in-hospital mortality. Pearson's Chi-square test for baseline categorical variables and one-way analysis of variance (ANOVA) for continuous variables were used to compare SBP categories versus patients baseline characteristics, treatment used, and outcomes. SBP categories were then dichotomized in five separate covariates (SBP<100 mmHg, SBP ≥100 to <120 mmHg, SBP≥120 to <140, SBP ≥140 to <160 mmHg and SBP ≥ 160 mmHg). Univariate Cox proportional hazard model was performed to assess the risk of outcomes for each 20 mmHg increment in SBP. Multivariable Cox proportional hazards regression model was performed to assess the risk of outcomes using baseline SBP values by 20 mmHg increments and then for each SBP category. Multivariable Cox proportional hazard regression analysis was performed that included SBP category adjusting for the following patient and hospital variables. Patient variables included: demographic (age and sex); medical history: current smoking, history of hypertension, history of diabetes mellitus, history of lipid disorders, presentation SBP category, HR at presentation >100 bpm and individual TRI score. Hospital variables included: medication usage (clopidogrel, ACE –inhibitors and beta blockers) and reperfusion therapy by percutaneous coronary intervention (PCI). Analysis was performed in the entire study cohort and then separately for STEMI and NSTE-ACS cohorts. For all analysis, a P value of <0.05 was considered statistically significant. All statistical evaluation was performed using STATA 11 (StataCorp. College Station, TX).

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Results

Patient baseline characteristics

Among the total study population the median baseline SBP was 140 mmHg. Table 1 shows the baseline characteristics by SBP categories. Patients with baseline SBP<100 mmHg were more likely to older and female, to have history of heart failure, previous cerebrovascular incidents, peripheral artery disease and chronic kidney disease. They were more likely to present with STEMI as qualifying event and had a higher risk profile at admission (Killip Class >1, higher baseline CRP levels, higher baseline Troponins levels and higher TRI score). In contrast, patients with baseline SBP≥160 mmHg were more likely to have higher rates of hypertension, higher body mass index and higher rates of ACE-inhibitors usage before 2 weeks prior to admission and were more likely to present with NSE-ACS. Patients in the range of baseline SBP≥140 to <160 mmHg were more likely to have cardiovascular risk factors (family history of coronary artery disease, history of lipid disorders, angina pectoris, previous MI and previous revascularization procedures).

In-hospital management

Table 2 shows the in-hospital therapeutic management by SBP categories. Patients with baseline SBP ≥140 to <160 mmHg, were less likely to be treated with acute phase medications (clopidogrel and heparins). Aspirin and heparins were more likely to be administered in patients with SBP≥160 mmHg (98% and 96.4%, respectively) and clopidogrel to patients with SBP≥100 to <120 mmHg. Reperfusion therapies were more likely to reserved to patients in patients with SBP≥140 to <160 and SBP≥160 mmHg. Beta-blockers, ACE-inhibitors and statins were more likely to be administered to patients in the higher SBP category.

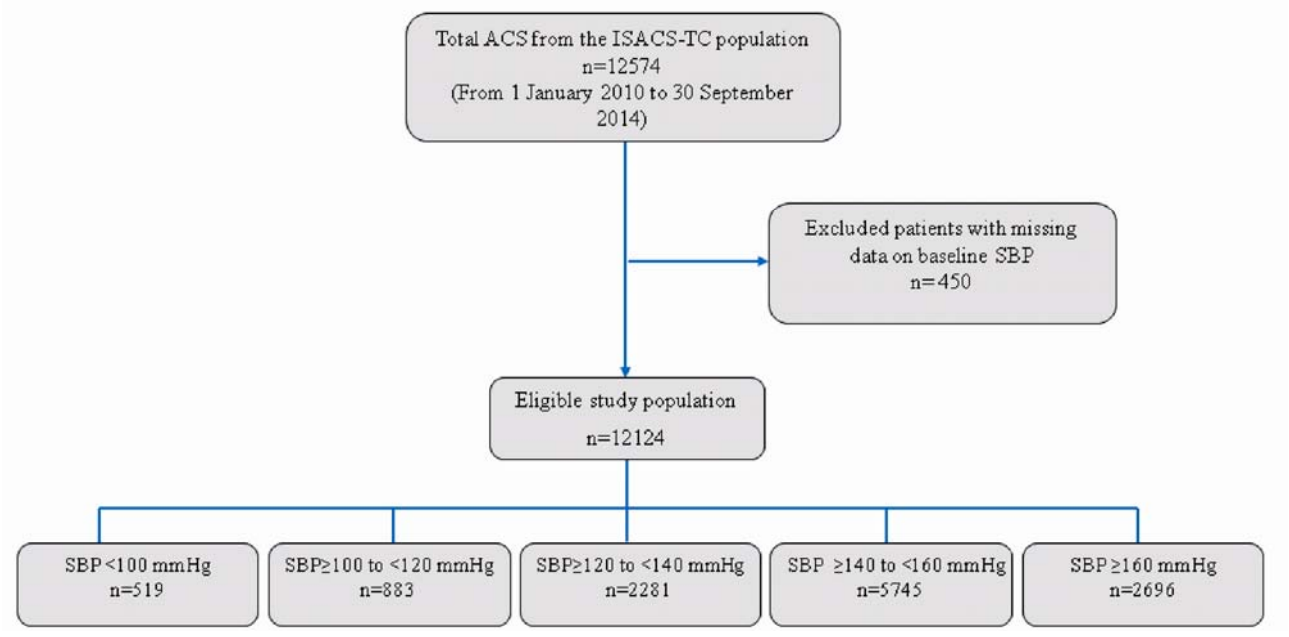

Figure 1. Diagram of inclusion criteria and distribution of patients sorted by baseline SBP values categories SBP= systolic blood pressure.

Table 1. Baseline characteristics sorted by baseline systolic blood pressure categories

Variable	Baseline systolic blood pressure, mmHg					P-Value*
	<100 n=519	≥100 to <120 n=883	≥120 to <140 n=2281	≥140 to <160 n=5745	≥160 n=2696	
Age, years	66.2 ± 12.1	62.5 ± 12.6	62.1 ± 12.4	62.1 ± 11.7	62.3 ± 11.5	<0.001
Female, n (%)	203 (39.1)	270 (30.6)	662 (29.0)	1841 (32.1)	869 (32.2)	<0.001
Family history of CAD, n (%)	132 (29.7)	185 (23.5)	528 (25.1)	2434 (44.9)	519 (20.6)	<0.001
Diabetes, n (%)	141 (28.9)	202 (23.8)	546 (24.8)	1421 (25.5)	690 (26.2)	0.25
Hypertension, n (%)	280 (55.8)	470 (54.3)	1392 (62.7)	3948 (69.9)	2015 (75.9)	<0.001
Lipid disorder, n (%)	119 (29.0)	237 (32.6)	685 (32.5)	2276 (44.1)	816 (34.6)	<0.001
Current smokers, n (%)	156 (31.5)	346 (40.4)	919 (41.5)	1861 (32.9)	989 (37.5)	<0.001
BMI	26.7 ± 4.8	26.4 ± 4.1	27.1 ± 4.1	27.2 ± 4.1	28.0 ± 4.4	<0.001
Angina pectoris, n (%)	93 (17.9)	129 (14.6)	419 (18.4)	1443 (25.1)	332 (12.3)	<0.001
History of heart failure, n (%)	47 (9.1)	74 (8.4)	178 (7.8)	205 (3.6)	144 (5.3)	<0.001
Previous MI, n (%)	92 (17.7)	122 (13.8)	383 (16.8)	1151 (20.0)	462 (17.1)	<0.001
Previous CVI, n (%)	45 (8.7)	43 (4.9)	101 (4.4)	293 (5.1)	124 (4.6)	0.002
Peripheral artery disease, n (%)	27 (5.2)	40 (4.5)	63 (2.8)	116 (2.0)	52 (1.9)	<0.001
Chronic kidney disease, n (%)	52 (11.4)	41 (5.9)	95 (5.5)	253 (5.9)	103 (7.7)	<0.001
Previous PCI, n (%)	45 (8.7)	47 (5.3)	189 (8.3)	1175 (20.5)	189 (7.0)	<0.001
Previous CABG, n (%)	15 (2.9)	17 (1.9)	46 (2.0)	207 (3.6)	35 (1.3)	<0.001
NSTE-ACS, n (%)	405 (78.0)	607 (68.7)	1375 (60.3)	3397 (59.1)	1474 (54.7)	<0.001
Killip Class > 1, n (%)	283 (74.9)	165 (31.4)	418 (32.2)	589 (15.4)	234 (23.9)	<0.001
Atypical baseline ECG, n (%)	16 (3.4)	47 (6.2)	146 (7.8)	154 (4.1)	100 (6.6)	<0.001
Baseline HR, bpm	84.7 ± 32.6	80.9 ± 24.8	79.6 ± 18.5	80.7 ± 12.5	82.7 ± 18.4	<0.001
TIMI Risk Index	47.3 ± 27.7	31.1 ± 16.8	25.5 ± 12.3	22.6 ± 9.2	19.3 ± 8.7	<0.001
Time from symptoms onset to admission<12 hours, n (%)	344 (70.6)	574 (71.3)	1455 (71.7)	3250 (70.5)	1599 (77.0)	<0.001
Time to presentation, median (IQR), minutes	240 (130-440)	270 (150-574.5)	275 (150-300)	300 (170-505)	280 (165-485)	0.009
Baseline serum creatinine, µmol/l	99.5 ± 53.8	92.6 ± 45.8	91.6 ± 52.1	87.3 ± 31.7	89.6 ± 53.2	<0.001
Baseline CRP, mg/dl	29.4 ± 34.7	21.7 ± 30.6	21.6 ± 27.3	19.8 ± 27.8	17.3 ± 24.9	0.06
Baseline Troponin T or I, mcg/l	17.4 ± 29.1	13.4 ± 25.3	13.1 ± 26.5	9.0 ± 21.9	6.9 ± 19.6	<0.001
Medication usage 2 weeks before index event						
Aspirin, n (%)	88 (28.0)	181 (25.8)	454 (27.1)	467 (28.1)	381 (26.6)	0.76
Beta blockers, n (%)	94 (30.2)	197 (27.9)	438 (26.3)	477 (28.7)	412 (28.7)	0.43
ACE-inhibitors, (%)	103 (32.5)	222 (31.3)	580 (34.7)	670 (40.2)	644 (44.4)	<0.001
Statins, n (%)	69 (22.3)	133 (19.0)	318 (19.1)	308 (18.7)	239 (16.8)	0.17

Data are presented as numbers (percentages) or mean ± SD, unless otherwise indicated. ***** P – values are obtained with the use of one-way analysis of variance (ANOVA) for continuous variables and Pearson's Chi-square test for categorical variables.

ACE = angiotensin converting enzyme; BMI = body mass index; CABG= coronary artery bypass graft; CAD= coronary artery disease; CRP = C-reactive protein; CVI= cerebro-vascular incidents (stroke and/or transient ischemic attack); ECG = electrocardiogram; HR = heart rate; IQR = interquartile range; MI = myocardial infarction; NSTE-ACS = non ST-segment elevation acute coronary syndromes; PCI = percutaneous coronary intervention; TIMI= Thrombolysis In Myocardial Infarction.

SPB and in-hospital mortality

The outcome endpoint was reached in 851 (7.0%) patients in the total study population. Figure 2 (Panel A) shows the incidence and risk of in-hospital mortality sorted by baseline SBP category. Patients with SBP<100 mmHg had the highest rates of in-hospital mortality (43.6%) as compared with the rest of SBP categories. A 20- mmHg increment in the baseline SBP was associated with a significant unadjusted reduction in the rates of in-hospital mortality (HR: 0.53; 95%CI: 0.50 –0.57). After adjustment for baseline, treatment covariates and TRI score (Table 3) a 20-mmHg increase in baseline SBP still remained associated with an approximately 30% risk reduction in in-hospital mortality (HR: 0.66; 95%CI: 0.62 –0.72). We repeated a separate analysis for each SBP category in the total study population (Figure 2, Panel B). The adjusted risk of in-hospital mortality showed a sharp decline in patients with SBP ≥ 140 to <160 mmHg (HR: 0.49; 95%CI: 0.40 – 0.59). This reduced risk was not observed in patients with SBP≥120 to <140 mmHg and SBP≥160 mmHg.

STEMI *versus* NSTE-ACS

NSTE-ACS was diagnosed in 4866 (40.2%) of the patients. The overall incidence of in-hospital mortality in the STEMI and NSTE-ACS cohorts were 8.2% and 5.2% respectively (p<0.001). In the overall sample, patients with baseline SBP ≥140 to <160 mmHg had lower rates of adjusted risk of in-hospital mortality. Similar findings were noted in the subgroup of patients with STEMI (HR: 0.47; 95%CI: 0.37-0.61) (Figure 2, Panel C and D). In the NSTE-ACS subgroup the risk was lower in patients both with baseline SBP ≥140 to <160 mmHg (HR: 0.52; 95%CI: 0.38-0.72) and baseline SBP ≥160 mmHg (HR: 0.54; 95%CI: 0.30–0.97) (Figure 2, Panel E and F).

Discussion

The major finding of the present study was that moderately high SBP on presentation was independently associated with reduced in-hospital mortality in ACS. The positive prognostic value of high SBP was even greater in NSTE-ACS.

Previous studies

Admission SBP is regarded as one useful factor for early risk stratification in acute myocardial infarction (AMI) patients. Accordingly, SBP is involved in most risk-scoring methods for patients with AMI [4-8]. Both the GRACE [7] and TIMI for STEMI risk score [4], consider low SBP as an adverse prognosticator. In the TIMI risk model high-risk patients (TIMI risk ≥5) not only have a mortality rate eight-times higher than the low-risk group, but also have an increased incidence of in-hospital adverse events such as heart failure and development of cardiogenic shock [4, 17]. The latter are clinical conditions having a SBP <100 mmHg. In the PROVE-IT-TIMI 22 trial [18] (PRavastatin Or atorVastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction) 4162 patients with ACS were categorized in 10-mmHg increments of blood pressure during follow-up: a U-shaped curve association was found between blood pressure and risk of future cardiovascular events, with the lowest event

Table 2. In-Hospital Management Sorted By Baseline Systolic Blood Pressure Categories

Variable	<100 n=519	≥100 to <120 n=883	≥120 to <140 n=2281	≥140 to <160 n=5745	≥160 n=2696	P-Value*
Baseline Systolic Blood Pressure, mmHg						
Acute medication usage at admission						
Aspirin, n (%)	471 (90.6)	834 (94.5)	2212 (97.0)	5465 (95.1)	2642 (98.0)	<0.001
Clopidogrel, n (%)	378 (72.8)	737 (83.5)	1309 (58.6)	2933 (52.0)	1918 (72.2)	<0.001
Heparins, n (%)	437 (84.9)	822 (93.9)	2119 (93.5)	4472 (78.4)	2587 (96.4)	<0.001
Reperfusion strategy						
Fibrinolysis, n (%)†	70 (14.6)	120 (15.8)	294 (15.4)	384 (8.6)	230 (14.9)	<0.001
PCI, n (%)	201 (39.4)	460 (52.7)	1199 (53.1)	3321 (58.6)	1653 (61.9)	<0.001
CABG, n (%)	5 (1.0)	14 (1.7)	45 (2.2)	159 (3.1)	106 (4.8)	<0.001
Other evidence based medication usage at admission and/or during hospital stay						
Beta blockers, n (%)	229 (44.6)	643 (73.4)	1737 (76.7)	4454 (78.1)	2143 (79.6)	<0.001
ACE-inhibitors, n (%)	274 (48.1)	611 (70.0)	1763 (77.8)	4495 (78.7)	2326 (86.7)	<0.001
Statins, n (%)	382 (74.3)	791 (90.4)	2119 (93.5)	5340 (93.5)	2591 (96.4)	<0.001

Data are presented as numbers (percentages).* P – values are obtained with the use of Pearson's Chi-square test for categorical variables. † Only for STEMI as qualifying event. ACE = angiotensin converting enzyme; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention.

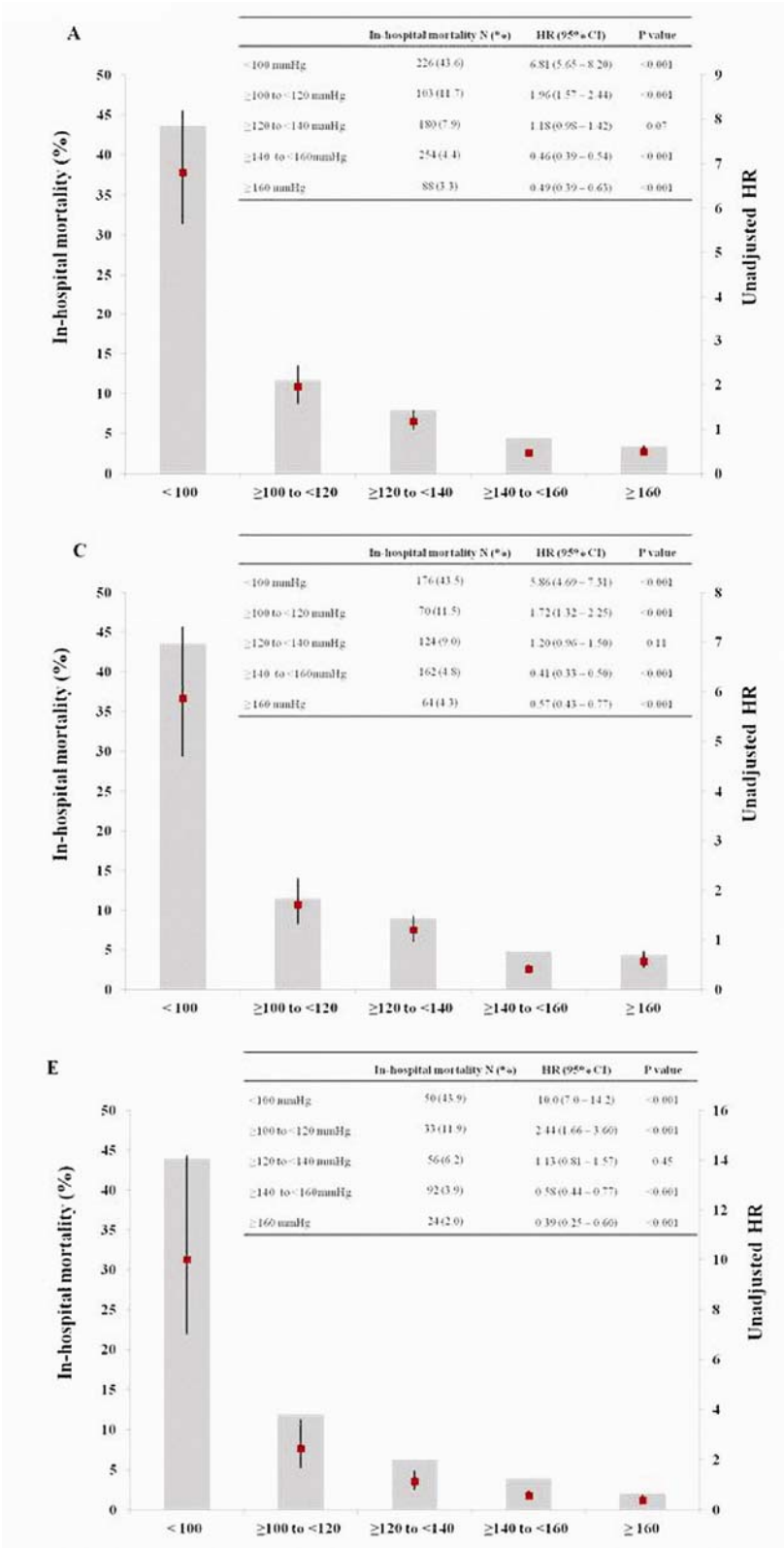

Figure 2. Risk of in-hospital mortality as a function of baseline SBP categories in the entire study cohort and sorted by ACS diagnosis. Panel A: Incidence and unadjusted risk of in-hospital mortality in the entire study cohort; Panel B: Adjusted risk of in-hospital mortality in the entire study cohort: Panel C: Incidence and unadjusted risk of in-hospital mortality in STEMI cohort; Panel D: Adjusted risk of in-hospital mortality in STEMI cohort; Panel E: Incidence and unadjusted risk of in-hospital mortality in NSTE-ACS cohort; Panel F: Adjusted risk of in-hospital mortality in NSTE-ACS cohort.
SBP = systolic blood pressure; STEMI = ST-segment elevation myocardial infarction; NSTE-ACS = non-ST-segment elevation acute coronary syndromes.

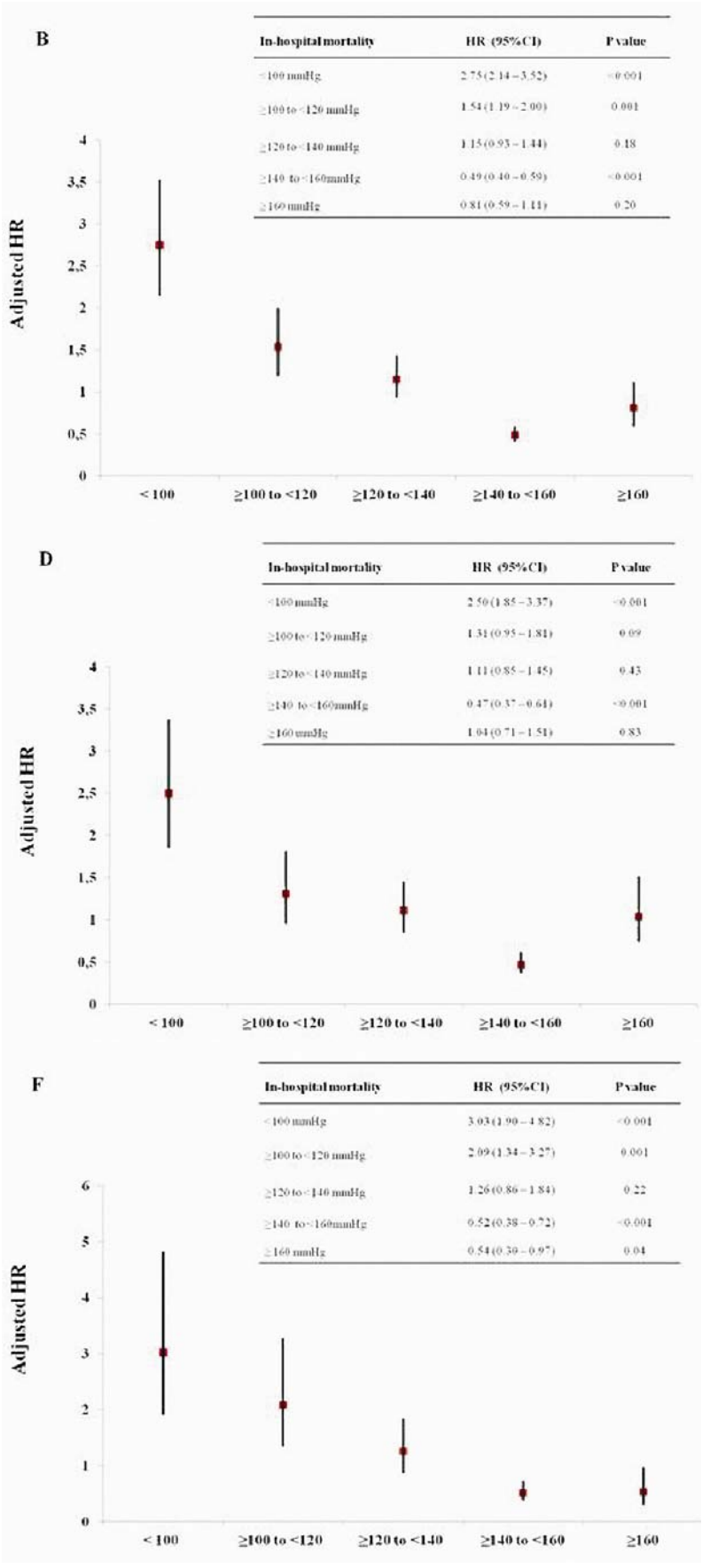

Figure 2 (continued)

Table 3. Adjusted Cox proportional hazard ratios of in-hospital mortality in the entire study cohort

In-hospital mortality	HR	95% CI	P-value
Baseline SBP, by 20-mmHg increment	0.66	0.61 – 0.72	<0.001
Age, years	1.02	1.01 – 1.04	<0.001
Female sex	1.13	0.94 – 1.36	0.17
Baseline HR >100 bmp	1.16	0.88 – 1.52	0.28
Current smoking	0.99	0.77 – 1.26	0.94
Hypertension	0.86	0.71 – 1.05	0.15
Diabetes	1.34	1.11 – 1.62	0.002
Lipid disorders	0.63	0.51 – 0.79	<0.001
TIMI Risk Index	1.30	1.12 – 1.50	<0.001
Clopidogrel usage at admission	0.77	0.61 – 0.96	0.02
PCI	0.84	0.68 – 1.04	0.12
ACE-inhibitors usage at admission	0.49	0.40 – 0.60	<0.001
Beta-blockers at admission	0.37	0.31 – 0.46	<0.001

ACE = angiotensin converting enzyme; HR = heart rate; PCI = percutaneous coronary intervention SBP = systolic blood pressure; TIMI = Thrombolysis In Myocardial Infarction.

rates in the SBP range of 130 to 140 mmHg, a flat curve for 110–130 mmHg SBP and the greatest event rates in the SBP range of < 110/70 mmHg. The latter finding strongly suggests that low pressures may be risky. However the study evaluated only "post baseline" blood pressure values during follow-up visits, not in-hospital measurements [18].

The present study

No study to date has assessed whether a relatively high SBP (i.e, SBP≥120 to <140 or even ≥160 mmHg) would have a favorable prognostic significance in a patient admitted for an ACS.

The present study showed that every 20 mmHg increase in baseline SBP has a hazard ratio of 0.66 for death, being, therefore, associated with approximately 30% reduction of in-hospital mortality. Antihypertensive medications used at admission, such as beta-blockers and ACE inhibitors were also independently associated with reduced in-hospital mortality [19] after adjusting for presenting SBP, which implies that risk scores incorporating SBP should be applicable for risk stratification regardless of use of concurrent use of powerful antihypertensive medications.

Mechanisms

The mechanism for which admission SBP ≥ 140 to <160 mmHg was associated with better in-hospital outcome remains uncertain. Patients with severe heart failure or cardiogenic shock present with low SBP. As SBP reflects either cardiac output or systemic peripheral resistance, we may hypothesize that high values at admission might indicate concurrent enhanced systemic resistance and preserved cardiac function after an ACS [20, 21]. This hypothesis is supported by the fact that the positive prognostic value of high SBP, in our study, was greater in NSTE-ACS than STEMI. Indeed, NSTE-ACS are a heterogeneous group. Most of these patients have partial or transient occlusion of a coronary artery and consequently less myocardial injury as compared with STEMI patients [22].

Conclusions

We cannot rule out that unmeasured confounders may have affected our results. We did not adjust our analysis for all possible cofounders. The lack of diastolic BP notably restricts our ability to assess the entire effect of blood pressure on mortality. Nevertheless, the present findings provide support for guideline recognition of a possible reduced risk of subsequent coronary events when SBP ≥ 140 to <160 mmHg.

Conflict of interest

The authors confirm that there are no conflicts of interest.

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