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Hypertension and acute coronary syndromes in Romania: data from the ISACS-TC registry

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There is little information on the incidence and prognostic significance of arterial hypertension (HTN) in acute coronary syndromes (ACSs), especially in the east European countries. We sought to investigate a registry of ACS patients in Romania, in order to better elucidate whether hypertensive patients are at higher risk of death and deserve a tailored approach for management and follow-up. The data of this study are a framework of the International Survey of Acute Coronary Syndromes in Transitional Countries (ISACS-TC) (ClinicalTrials.gov, NCT01218776). The present analysis focused on 2286 retrospective patients admitted to 23 hospitals in Romania with a diagnosis of ACS. Among 1450 hypertensive patients, 64.5% were admitted with a diagnosis of STelevation myocardial infarction (STEMI), while the remaining was admitted with a diagnosis of non-STEMI (NSTEMI). When compared with non-hypertensive patients, hypertensive patients were older (mean age 60.3 vs. 66.7 years, $P < 0.001$), were prevalently female (25.8% vs. 35.5%, $P < 0.001$), and had higher rates of cardiovascular risk factors as well as higher rates of prior myocardial infarction (11.2% vs. 18.3%, $P < 0.001$). Additionally, they had higher rates of prior stroke (4.2% vs. 11.7%, $P < 0.001$) and chronic heart failure (11.5% vs. 18.4%, $P < 0.001$). Despite this adverse clinical profile, hypertensive patients were less likely be to be admitted with Killip class $\geq$2 (23.1% vs. 26.6%, $P < 0.001$) but they were more likely to be discharged with NYHA class $\geq$III (10.6% vs. 7.1%, $P < 0.006$). There were significant higher rates of unadjusted in-hospital mortality among hypertensive older ($>$65 years) patients with both STEMI and NSTEMI. Hypertensive ACS patients in Romania represent a higher risk group, since they are more often discharged with NYHA class $\geq$ III, are older and have an adverse clinical profile. In the elderly, the outcomes of the hypertensive patients are worse than non-hypertensive patients.

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Introduction

Arterial chronic hypertension (HTN) is a well-known cardiovascular risk factor for development of atherosclerosis. Atherosclerosis, in turn, can progress to acute coronary syndrome (ACS). From all the registries and the data available up to now, hypertensive patients with ACS are more likely to be older and female and to have a higher prevalence of comorbidities. Data on the prognostic role of a pre-existing hypertensive state in ACS patients are contradictory and come mostly from old trials and registries, before the era of thrombolysis.[1] In patients with acute myocardial infarction (AMI), the prevalence of history of HTN varies from 31 to 59%.[2,3] On the contrary, it is not clear whether previously known hypertensive patients have an increased rate of adverse outcomes after non-ST elevation AMI (NSTEMI).[4,5]

There is little information on ACS in the East European countries.[6,7] The East European countries have reported high prevalence of HTN.[8] We sought to investigate a registry of ACS patients in Romania, in order to better elucidate whether hypertensive patients are at higher risk of death and deserve a tailored approach for management and follow-up.

Methods

Study population

The study population consisted of 2286 retrospective Romanian patients admitted with a diagnosis of ACS in 23 Romanian hospitals reporting data to the ISACS-TC registry (International Survey of Acute Coronary Syndromes in Transitional Countries).[9] Data collection was according to the ISACS-TC protocol (ClinicalTrials.Gov, NCT01218776).

Statistical analysis

Descriptive statistics were used to report the data. Values are expressed as mean $\pm$ SD for continuous variables and total number (percentages) for categorical variables. The study population was divided into two groups by the presence of HTN. Non-hypertensive and hypertensive patients were also stratified in age groups ($<$45, 45–65, and $>$65 years, respectively). Differences between groups were analysed using Pearson's chi-square test for categorical variables or the two-sample *t*-test con continues variables.

For all analysis, statistical significance was defined as a value of $P < 0.05$. Statistical evaluation was performed using STATA Version 11 statistical software system.

Results

Of the 2286 Romanian patients with ACS from the ISACS-TC registry, 1450 were hypertensive, accounting for a 63.4% prevalence of pre-existent hypertensive state.

There were several significant differences between hypertensive and non-hypertensive Romanian ACS patients in the current study.

Demographic factors

Hypertensive patients with ACS were significantly older (on average, 6.4 years more) had more traditional risk factors and were more frequently females (*Table 1*).

Hypertensive and non-hypertensive ACS patients were stratified for age groups ($<$45, 45–65, and $>$65 years). Female gender was more prevalent in the older age group (15.6, 25.2, and 43.1%, respectively, $P < 0.001$), while male gender was more prevalent in the youngest age group (84, 82.7, and 65.5%, respectively, $P < 0.001$; *Table 2*).

Comorbidities

Diabetes and hypercholesterolaemia were significantly more frequent among the hypertensive ACS patients compared with non-hypertensive patients. The mean body mass index and both the current and former smoker status were similar in both groups (*Table 1*).

Hypertensive ACS patients had a higher prevalence of prior stroke, prior MI, peripheral artery disease, chronic heart failure, kidney failure, and prior myocardial revascularization procedures (*Table 1*).

Although the history of kidney failure was more prevalent among hypertensive ACS patients, mean serum creatinine levels were similar between hypertensive and non-hypertensive patients without any significant differences among different age groups (*Tables 1* and *2*).

Index event

Of the 2286 ACS patients enrolled, ST elevation myocardial infarction (STEMI) was the clinical presentation in 1632 cases accounting for 71.4% of the overall study population; the remaining 654 patients were NSTEMI. STEMI presented more frequently among the non-hypertensive ACS patients (81.1% vs. 64.5%, $P < 0.001$). Conversely, NSTEMI was more frequently among the hypertensive ACS patients (34.6%, vs. 18.2%, $P < 0.001$).

Time from symptoms onset to admission

The majority of ACS patients (77.3%) were admitted to hospital within 12 h from symptom onset. Hypertensive ACS patients arrived within 12 h more frequently (79.1%) than non-hypertensive ACS patients (*Table 1*). Both in hypertensive and in non-hypertensive ACS patients, the majority of late comers belonged to $>$65 years age group, while the majority of timely arrived patients were younger ($<$45 years age group; *Table 2*).

Clinical characteristics

There were no differences between the two groups of ACS patients in terms of chest pain at presentation for the index event. On the opposite, there were significant differences between the two groups regarding both occurrence of arrhythmias and conduction disturbances and Killip class

Table 1 Baseline characteristics stratified in by the presence of arterial hypertension

	Not-hypertensive ($n = 836$)	Hypertensive ($n = 1450$)	*P*-value
Demographic factors			
Age (years)	60.3 ± 14.2	66.7 ± 11.7	<0.001
Female	216 (25.8)	514 (35.5)	<0.001
Cardiovascular risk factors			
BMI	28.2 ± 15.7	29 ± 13.9	0.2
Diabetes	151 (18.1)	390 (26.9)	<0.001
Hypercholesterolaemia	84 (10.1)	326 (22.5)	<0.001
Smokers	279 (33.4)	416 (28.7)	0.13
Formers smokers	128 (15.3)	238 (16.4)	0.13
Family history of CAD	65 (7.78)	129 (8.9)	0.009
Clinical history			
Prior stroke	35 (4.2)	172 (11.7)	<0.001
Prior MI	94 (11.2)	266 (18.3)	<0.001
Prior CABG	7 (0.9)	26 (1.8)	0.006
Prior PCI	26 (3.1)	66 (4.6)	0.025
Peripheral artery disease	49 (5.9)	125 (8.2)	<0.001
Chronic heart failure	96 (11.5)	267 (18.4)	<0.001
Chronic kidney disease	31 (3.7)	117 (8.0)	<0.001
Serum creatinine (μmol/L)	105.8 ± 79.1	109.9 ± 78.7	0.2
Index event type			
STEMI	684 (81.8)	948 (65.4)	<0.001
NSTEMI	152 (18.2)	502 (34.6)	<0.001
Chest pain at presentation	817 (97.6)	1431(98.7)	0.16
Time from symptoms onset to admission <12 h	620 (74.2)	1147 (79.1)	0.007
Killip class ≥ 2	222 (26.6)	335 (23.1)	<0.001
Arrhythmias at presentation			
Supraventricular arrhythmias	63 (7.5)	163 (11.2)	0.02
Ventricular fibrillation	6 (0.7)	9 (0.6)	0.02
AV blocks	55 (6.6)	95 (6.5)	0.73
Heart rate (b.p.m.)	82.2 ± 25.7	84.2 ± 24	0.06
SBP (mmHg)	128.9 ± 40.2	141.4 ± 32	<0.001
Biomarkers			
Troponin T or I (μg/L)	10.1 ± 25.4	10.5 ± 25.5	0.7
CK at peak values (U/L)	1218.7 ± 1388.2	1367.4 ± 1760.9	0.03
CK-MB at peak values (U/L)	153.9 ± 248.8	178.3 ± 286.6	0.04
Therapy at index event			
Medical therapy	487 (58.2)	1019 (70.3)	<0.001
Fibrinolysis	279 (33.4)	308 (21.2)	<0.001
Primary/urgent PCI	70 (8.4)	123 (8.5)	<0.001
Outcomes			
Haemodynamic instability	226 (27.0)	383 (26.4)	0.9
In-hospital complications	71 (8.5)	138 (9.5)	0.53
Recurrent ischaemia	35 (4.2)	60 (4.1)	0.93
Left ventricular ejection fraction (%)	43.6 ± 9.09	43.7 ± 9.5	0.8
NYHA class ≥ III	59 (7.1)	153 (10.6)	0.006
In-hospital mortality	96 (11.5)	153 (10.6)	0.49
In-hospital mortality according to the AMI type			
STEMI	71 (10.4)	108 (11.4)	0.518
NSTEMI	25 (16.5)	45 (9.0)	0.009

Values are expressed as numbers, *n* (%) or mean ± SD. BMI, body mass index; CAD, coronary artery disease; AMI, acute myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; AV block, atrium ventricular block; SBP, systolic blood pressure; NYHA, New York Heart Association. Supraventricular arrhythmias = atrial fibrillation and atrial flutter; haemodynamic instability = composite of cardiogenic shock, hypovolemic shock, and acute pulmonary oedema; in-hospital complications = composite of cardiac arrest, stroke, bleeding, and intracranial haemorrhage.

at presentation. Supraventricular arrhythmias (such as atrial fibrillation or atrial flutter) and left bundle branch block were more frequently among hypertensive ACS patients, whereas Killip class ≥ 2 and ventricular arrhythmias (ventricular fibrillation) were more frequently among non-hypertensive patients. There were no differences between the two groups regarding AV blocks (*Table 1*).

Table 2 Baseline characteristics in non-hypertensive and hypertensive patients, stratified by age groups

	Non-hypertensive ($n = 836$)			Hypertensive ($n = 1450$)			*P*-value
	<45 years ($n = 125$)	45–65 years ($n = 382$)	>65 years ($n = 329$)	<45 years ($n = 45$)	45–65 years ($n = 552$)	>65 years ($n = 853$)	
Female	20 (16.0)	66 (17.3)	130(39.5)	7 (15.6)	139 (25.2)	368 (43.1)	<0.001
Diabetes	13 (10.4)	69 (18.1)	69 (21.0)	8 (17.8)	167 (30.3)	215 (25.2)	<0.001
Hypercholaesterolemia	15 (12.0)	42 (11.0)	27 (8.2)	9 (20.0)	142 (25.7)	175 (20.5)	<0.001
Smokers	63 (50.4)	140 (36.7)	76 (23.1)	21 (46.7)	202 (36.6)	193 (22.6)	<0.001
Family history of CAD	16 (12.8)	36 (9.4)	13 (3.9)	7 (15.6)	70 (12.7)	52 (6.1)	<0.001
Prior stroke	0 (0)	7 (1.8)	28 (8.5)	3 (6.7)	50 (9.1)	119 (14.0)	<0.001
Prior MI	10 (8.0)	39 (10.2)	45 (13.7)	6 (13.3)	79 (14.3)	181 (21.2)	<0.001
Prior CABG	1 (0.8)	6 (1.6)	1 (0.3)	1 (2.2)	11 (2.0)	14 (1.6)	<0.001
Prior PCI	4 (3.2)	11 (2.9)	11 (3.3)	1 (2.2)	23 (4.2)	42 (5.0)	<0.001
Peripheral artery disease	4 (3.2)	14 (3.7)	31 (9.4)	1 (2.2)	45 (8.2)	79 (9.3)	<0.001
Chronic heart failure	7 (5.6)	33 (8.6)	56 (17.0)	2 (4.5)	56 (10.1)	209 (24.5)	<0.001
Chronic kidney disease	1 (0.8)	4 (1.0)	26 (7.9)	1 (2.2)	26 (4.7)	90 (10.6)	<0.001
Serum creatinine (μmol/L)	110.7 $\pm$ 107.3	100.2 $\pm$ 72.3	110.2 $\pm$ 74	124 $\pm$ 122.7	109.8 $\pm$ 88.3	109.2 $\pm$ 68.3	0.4
Index event							
STEMI	113 (90.4)	321 (84.0)	250 (76.0)	29 (64.4)	393 (71.2)	526 (61.7)	<0.001
NSTEMI	12 (9.6)	61 (16.0)	79 (24.0)	16 (35.6)	159 (28.8)	327 (38.4)	<0.001
Killip Class $\geq$ 2	22 (17.6)	95 (24.9)	105 (31.9)	6 (13.3)	107 (19.4)	222 (26.0)	<0.001
Heart rate (b.p.m.)	82.8 $\pm$ 21.4	80 $\pm$ 22.2	83.9 $\pm$ 30.2	84.6 $\pm$ 19.6	82.5 $\pm$ 24.5	85 $\pm$ 24.3	0.16
SBP (mmHg)	126.9 $\pm$ 22.5	128.3 $\pm$ 26.0	130 $\pm$ 56.3	148 $\pm$ 31	142.4 $\pm$ 31.2	140 $\pm$ 32.3	0.1
Arrhythmias at presentation	5 (4.0)	49 (12.8)	86 (26.1)	3 (6.7)	54 (9.8)	251 (29.4)	<0.001
Time from symptoms onset to admission <12 h	96 (76.8)	294 (77.0)	230 (70)	39 (86.7)	440 (79.7)	668 (78.3)	0.01

Values are expressed as numbers, *n* (%) or mean $\pm$ SD. CAD, coronary artery disease; MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; STEMI, ST elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; SBP, systolic blood pressure.

Arrhythmias and conduction disturbances and Killip class ≥ 2 at presentation were more frequently recorded among >65 years age group (*Table 2*).

Although mean troponin T or I levels were similar between the two groups, both total CK and CK-MB levels were significantly higher among hypertensive ACS patients (*Table 1*).

Treatment

Medical therapy before admission for the index event

Hypertensive ACS patients received more frequently both antihypertensive drugs [such as Angiotensin Converting Enzyme Inhibitors (ACEIs), Angiotensin Receptors Blockers (ARBs), Calcium Channels Blockers (CCBs)] and anti-ischaemic medications [such as Beta-blockers (BBs), antiplatelet, and statins) than non-hypertensive ACS patients. After adjusting for age groups, it should be noticed that younger hypertensive ACS patients more frequently used only ARBs and clopidogrel, while aspirin, BBs, ACEIs, CCBs, and statins were more frequently used by the older hypertensive ACS patients (*Tables 1* and *3*).

Revascularization therapy at the index event

Revascularization therapy at the index event using primary or urgent PCI was more frequently performed in hypertensive ACS patients than in non-hypertensive ACS patients (70.3% vs. 58.2%, $P < 0.001$; *Table 1*). Accordingly, fibrinolysis was more frequently applied for non-hypertensive ACS patients. Myocardial revascularization therapy was used mainly in the younger patients (*Table 3*) in both the hypertensive and non-hypertensive ACS groups.

In-hospital therapy and medications prescribed at discharge

There were no significant differences between the hypertensive and non-hypertensive groups regarding treatment with the majority of medications during hospitalization and at discharge. The only significant differences between the two groups, regarding both therapies during hospitalization and at discharge, were related to ACEIs, ARBs, CCBs, diuretics, and statins. These drugs were more frequently used in hypertensive ACS patients (*Table 3*).

Outcomes

There were no significant differences between hypertensive and non-hypertensive ACS patients in terms of haemodynamic instability (such as cardiogenic or hypovolemic shock or acute pulmonary oedema) or in-hospital complications (such as cardiac arrest, stroke, bleeding events, or intracranial haemorrhage). In addition, there were no significant differences in mean left ventricular ejection fraction between the two groups (non-hypertensive: 43.6 ± 9.09% vs. hypertensive: 43.7 ± 9.5%, $P = 0.8$). The majority of NYHA class ≥ III cases at discharge occurred among hypertensive ACS patients. Recurrent ischaemic events took place similarly between the two groups (*Table 1*).

NSTEMI occurred more frequently among older hypertensive patients (>65 years), while STEMI was more frequent in younger non-hypertensive patients (≤65 years; *Table 2*).

There were significant higher rates of unadjusted in-hospital mortality among hypertensive older (>65 years) patients with both STEMI (24.0% vs. 49.7%, $P < 0.001$) and NSTEMI (27.1% vs. 51.4%, $P = 0.001$) (*Figure 1*).

Discussion

Our study revealed a 63.4% prevalence of HTN among ACS patients. This value is greater than that reported in a general population of Romanian people (40.4%).[10] Previous work focused mainly on patients with STEMI submitted to primary PCI,[11,12] in which a previous history of HTN ranged from 30 to 33%. The SYMPHONY trial[13] showed in STEMI patients a prevalence of HTN of ∼50%. More recently, the Spanish registry (PRIMVAC) reported a 46% prevalence of HTN in STEMI patients.[14] Again, a further small study performed in 856 STEMI patients all submitted to primary PCI found that a previous history of HTN was detectable in 50.6% of patients.[12] In our and other studies performed in the overall population of ACS, chronic HTN was the most prevalent risk factor being detectable in almost two-thirds of NSTEMI patients.[15] This finding may be justified by the fact that NSTEMI patients are more prevalently older and women compared with STEMI patients, and elderly and female sex is often undertreated.[16]

In our population, we included both STEMI and NSTEMI patients. In keeping with previous observations, our hypertensive patients with ACS were older than non-hypertensive patients and were more frequently females, especially in the older age group (>65 years). Hypertensive patients had significantly more comorbidities, like diabetes and hypercholesterolaemia, compared with non-hypertensive patients. They arrived earlier to hospital. Nevertheless, they had history of complications like stroke, myocardial infarction, peripheral artery disease, myocardial revascularization significantly more frequent than non-hypertensive patients.

In the KAMIR study, 48% of STEMI patients had HTN: at multivariate analysis, a history of HTN independently contributed to higher in-hospital but not to 1-year mortality. This was mainly related to the coexistence of other risk factors (old age, higher Killip class, multivessel disease).[17] Recurrent myocardial ischaemia, multivessel disease, and complex lesions in coronary angiography are among the factors which have been proved to be associated with poor outcomes in hypertensive patients.[18,19] Unfortunately, only few of our patients underwent urgent revascularization. It should be noted, however, recurrence of ischaemia was similar between hypertensive and non-hypertensive patients, which may explain that in-hospital mortality rates of patients were similar between groups.

In our study, acute supraventricular arrhythmias were more frequent in the non-hypertensive group.

There were significant higher rates of unadjusted in-hospital mortality among hypertensive older (>65 years) patients with both STEMI and NSTEMI. Age is by far the most important risk factor for ACS. Yet, a high systolic BP is an independent risk factor for coronary artery disease. Thus, the effects of aging cannot be separated

Table 3 Therapy in non-hypertensive and hypertensive patients, stratified by age groups

	Non-hypertensive ($n = 836$)			Hypertensive ($n = 1450$)			*P*-value
	<45 years ($n = 125$)	45–65 years ($n = 382$)	>65 years ($n = 329$)	<45 years ($n = 45$)	45–65 years ($n = 552$)	>65 years ($n = 853$)	
Therapy before admission							
Aspirin	10 (8.0)	37 (9.7)	46 (14.0)	7 (15.6)	144 (26.1)	287 (33.7)	<0.001
Clopidogrel	1 (0.8)	11 (2.9)	4 (1.2)	2 (4.5)	29 (5.3)	37 (4.3)	0.02
Beta-blockers	5 (4.0)	45 (11.8)	46 (14.0)	11 (24.4)	172 (31.2)	299 (35.1)	<0.001
ACE inhibitors	2 (1.6)	18 (4.7)	45 (13.7)	8 (17.8)	201 (36.4)	387 (45.4)	<0.001
ARBs	2 (1.6)	2 (0.5)	3 (0.9)	3 (6.7)	16 (2.9)	37 (4.3)	<0.001
CCB	3 (2.4)	11 (2.9)	11 (3.3)	1 (2.2)	48 (8.7)	132 (14.5)	<0.001
Statins	7 (5.6)	35 (9.2)	31 (9.4)	9 (20.0)	118 (21.49)	189 (22.2)	<0.001
Therapy at index event							
Fibrinolysis	51 (40.8)	153 (40.0)	75 (22.8)	12 (26.7)	177 (32.0)	119 (14.0)	<0.001
Primary or urgent PCI	20 (16.0)	36 (9.4)	14 (4.3)	8 (17.8)	59 (10.7)	56 (6.6)	<0.001
In-hospital therapy							
Aspirin and/or clopidogrel	122 (97.6)	376 (98.4)	313 (95.1)	45 (100)	540 (97.8)	827 (96.9)	0.18
Heparins	124 (99.2)	374 (97.9)	309 (93.9)	44 (97.8)	542 (98.2)	811 (95.1)	0.001
Beta- blockers	117 (93.6)	332 (86.9)	239 (72.6)	42 (93.3)	513 (92.9)	671 (78.7)	<0.001
ACE inhibitors or ARBs	109 (87.2)	306 (80.1)	231 (70.2)	42 (93.3)	501 (90.8)	727 (85.2)	<0.001
CCBs	12 (9.6)	9 (2.4)	12 (3.7)	3 (6.7)	40 (7.3)	77 (9.0)	0.001
Statins	117 (93.6)	332 (86.9)	259 (78.7)	41 (91.1)	522 (94.6)	763 (89.5)	<0.001
Therapy at discharge							
Aspirin and/or clopidogrel	123 (98.4)	338 (88.5)	255 (77.5)	40 (88.9)	509 (98.2)	688 (80.7)	<0.001
ACE inhibitors or ARBs	102 (81.6)	289 (875.7)	219 (66.6)	40 (88.9)	471 (85.3)	653 (76.6)	<0.001
Beta-blockers	114 (91.2)	318 (83.3)	223 (67.8)	39 (86.7)	483 (87.5)	613 (71.79	<0.001
CCB	11 (8.8)	14 (3.7)	18 (5.5)	3 (6.7)	41 (7.4)	82 (9.69	0.01
Statins	114 (91.2)	314 (82.2)	232 (70.5)	39 (86.7)	493 (89.3)	662 (77.6)	<0.001
Diuretics	6 (4.8)	41 (10.7)	76 (23.1)	5 (11.19	141 (25.5)	285 (33.4)	<0.001

Values are expressed as numbers, *n* (%) or mean ± SD.
ACE, angiotensin-converting enzyme; ARBs, angiotensin receptors blockers; CCBs, calcium-channel blockers.

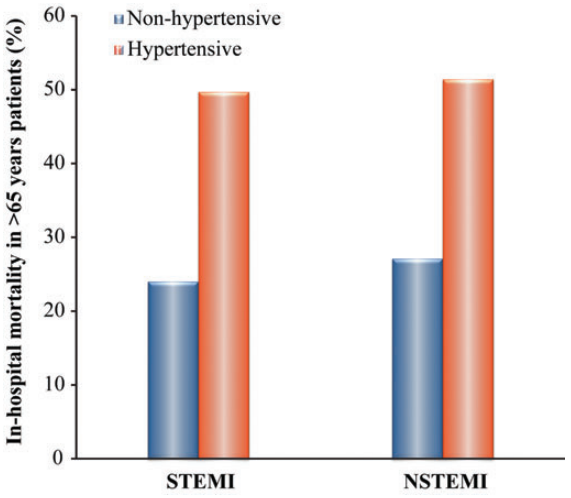

Figure 1 In-hospital mortality in older (>65 years) non-hypertensive (blue) and hypertensive (red) STEMI and NSTEMI patients. Among 329 non-hypertensive patients and 853 hypertensive patients aged >65, in-hospital mortality occurred in 43 (24.0%) and 89 (49.7%), $P < 0.001$ STEMI patients, respectively, and 19 (27.1%) and 36 (51.4%), $P = 0.001$, NSTEMI patients, respectively. STEMI, ST elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction.

easily from those of blood pressure, although our data showed an increased mortality in those patients with history of HTN.

Limitations

One of the main limitations of our study is that the correlation between BP and prognosis is based on a clinical history of HTN.[20,21] We have not available data on BP during hospital stay measurements.

Conclusions

ACS patients with HTN in Romania in the ISACS-CT registry represent a subset at higher risk for death, since they are more often older, females and with more comorbidities. Their outcome in-hospital during admission for ACS was not different form non-hypertensives, but they tended to have less severe heart failure. Revascularization and optimal medical treatment was used less than expected, presumably due to older age and comorbidities.

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