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Original Article

Trends in management and outcome of patients with non-ST elevation acute coronary syndromes and peripheral arterial disease

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ABSTRACT

Objective: Patients with non ST-segment elevation acute coronary syndromes (NSTE-ACS) and peripheral arterial disease (PAD) present a worse prognosis compared to those without PAD. We sought to describe contemporary trends of in-hospital management and outcome of patients admitted for NSTE-ACS with associated PAD.
Methods: We analyzed data from 6 Italian nationwide registries, conducted between 2001 and 2014, including consecutive NSTE-ACS patients.
Results: Out of 15,867 patients with NSTE-ACS enrolled in the 6 registries, 2226 (14.0%) had a history of PAD. As compared to non-PAD patients, those with PAD had significantly more risk factors and comorbidities (all $p < 0.0001$) that increased over time. Patients with PAD underwent less frequently coronary angiography (72.0% vs 79.2%, $p < 0.0001$) and percutaneous coronary intervention (PCI, 42.9% vs 51.8%, $p < 0.0001$), compared to patients without PAD. Over the years, a progressive and similar increase occurred in the rates of invasive procedures both in patients with and without PAD (both p for trend < 0.0001). The crude in-hospital mortality rate did not significantly change over time (p for trend = 0.83). However, as compared to 2001, the risk of death was significantly lower in all other studies performed at different times, after adjustment for multiple comorbidities.. At multivariable analysis, PAD on admission was an independent predictor of in-hospital mortality [odds ratio (OR): 1.75; 95% confidence intervals (CI): 1.35–2.27; $p < 0.0001$].
Conclusions: Over the 14 years of observation, patients with PAD and NSTE-ACS exhibited worsening baseline characteristics and a progressive increase in invasive procedures. Whereas crude in-hospital mortality did not change over time, we observed a significant reduction in comorbidity-adjusted mortality, as compared to 2001.

1. Introduction

Prior studies have shown that patients with non ST-segment elevation acute coronary syndromes (NSTE-ACS) and prior peripheral arterial disease (PAD) are often undertreated during their index admission and present worse in-hospital and long-term outcomes compared to patients without PAD [1–6]. Despite these findings, there are no data available describing contemporary and changing trends in the epidemiology, treatments and in-hospital clinical event rates for patients with NSTE-ACS and concomitant PAD.

We therefore used the database of nationwide surveys to describe the evolution of in-hospital management and outcome for NSTE-ACS

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patients with PAD admitted to cardiac care units (CCUs) from 2001 to 2014 in Italy.

2. Methods

Six prospective registries designed by the Italian Association of Hospital Cardiologists (ANMCO) in patients with ACS were conducted in Italy between 2001 and 2014: BLITZ in 2001 [7], BLITZ-2 in 2003 [8], IN-ACS Outcome (Italian Network on Acute Coronary Syndromes Outcome) in 2006–2007 [9], BLITZ-4 in 2009–2010 [10], MANTRA (Management of patients with ACS in the real world practice in Italy: an outcome research study focused on the use of ANTithRombotic Agents) in 2010 [11], and EYESHOT (EmploYEd antithrombotic therapies in patients with acute coronary Syndromes HOspitalized in iTalian cardiac care units) in 2013–2014 [12]. All surveys were nationwide and included patients with ACS consecutively admitted to the participating CCUs during a pre-specified period (few weeks for all the BLITZ registries and for EYESHOT registry and 1 year for IN-ACS Outcome and MANTRA). The methods used for each registry have been described previously [7–12]. Briefly, their primary objectives were to evaluate the clinical characteristics, management, and outcomes of consecutive patients with ACS admitted to Italian CCUs, using a catchment method broad enough to provide data representative of the entire country. Participation in the various registries had been offered to all institutions in BLITZ surveys and EYESHOT and to a representative sample of CCUs (balanced by geographical region and hospital complexity) in IN-ACS Outcome and MANTRA. Physicians were instructed that participation in the registries should not affect clinical care or management. Informed consent was obtained from all patients who were aware of the nature and aims of the registries. Local Institutional Review Boards were informed of the study according to the Italian rules and approved the protocol.

2.1. Data collection

Data on baseline characteristics, including demographics, risk factors and medical history, were collected as previously described [7–12]. Information on the use of cardiac procedures, including coronary angiography, type of revascularization therapy (if any), use of medications during hospitalization and at hospital discharge, and in-hospital major clinical events, were recorded. For the present analysis, we focused on NSTE-ACS patients with a history of PAD on admission, comparing them to NSTE-ACS patients without PAD on admission.

The definitions of inclusion criteria and outcome events were consistent throughout the surveys. All patients with a clinical presentation suggestive of acute myocardial ischemia, with or without acute ischemic changes on the ECG were define as NSTE-ACS [13]. PAD was defined as history of PAD documented in the medical record or history of claudication; amputation for arterial insufficiency; aorta-iliac occlusive disease reconstruction surgery; carotid/vertebral artery disease; peripheral vascular bypass surgery, angioplasty, or stent; documented abdominal aortic aneurysm, aneurysm repair or stent; and documented positive noninvasive testing such as abnormal ankle-brachial index or pulse volume recording.

Re-infarction during initial hospitalization was diagnosed in the presence of new ischemic symptoms and a re-elevation of biochemical myocardial necrosis markers with or without concurrent ECG changes. Major bleeding was classified according to the Thrombolysis In Myocardial Infarction (TIMI) criteria [14]. Stroke was identified as an acute neurologic deficit lasting > 24 h and affecting the ability to perform daily activities with or without confirmation by imaging techniques.

All data were collected using a case report form (CRF) at the participating centers and entered in a centralized database located at the ANMCO Research Center (Florence, Italy). By using a validation plan integrated in the data entry software, data were checked with data queries for missing or contradictory entries and values out of the normal range. The data were also centrally audited at the coordinating center.

2.2. Statistical analysis

Categorical variables were reported as numbers and percentages and compared by Chi-square test, whereas continuous variables were reported as means and standard deviations and compared by *t*-test or analysis of variance (ANOVA), if normally distributed, or by Mann-Whitney *U* test and Kruskal − Wallis test, if not.

Temporal trends were tested using the Cochran-Armitage test for binary variables and the Kendall Tau rank correlation coefficient with the Jonckheere-Terpstra test for continuous variables. A multivariable analysis (logistic regression) was performed to estimate the risk of in-hospital mortality over time in NSTE-ACS patients, adjusting for study cohort (year), gender, age, diabetes, history of heart failure, prior stroke/TIA, PAD, chronic renal dysfunction, type of hospital (with or without cath lab facilities), geographic area, systolic blood pressure, heart rate, Killip class and atrial fibrillation at admission. In case of categorical variables, when more than two categories were present, dummy variables were introduced to define a reference group (i.e, year 2001 for study cohort, and north for geographic area).

All tests were 2-sided; a p value < 0.05 was considered statistically significant. All analyses were conducted with SAS system software version 9.2 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient characteristics

Out of 15,867 patients with NSTE-ACS enrolled in the 6 registries, 2226 (14.0%) had history of PAD on admission. The rates of patients with PAD enrolled in each registry are reported in Fig. 1. As compared to patients without PAD, those with PAD were significantly older, less frequently women, had significantly more diabetes, hypertension and chronic kidney dysfunction, as well as a more prevalent history of angina, myocardial infarction, coronary revascularization and stroke/TIA. Patients with PAD also had worse hemodynamic condition on admission, including higher heart rate, lower ejection fraction and higher rate of Killip class IV, and less frequently received antiplatelet therapies during hospitalization (Table 1).

3.2. Clinical characteristics of patients with PAD over time

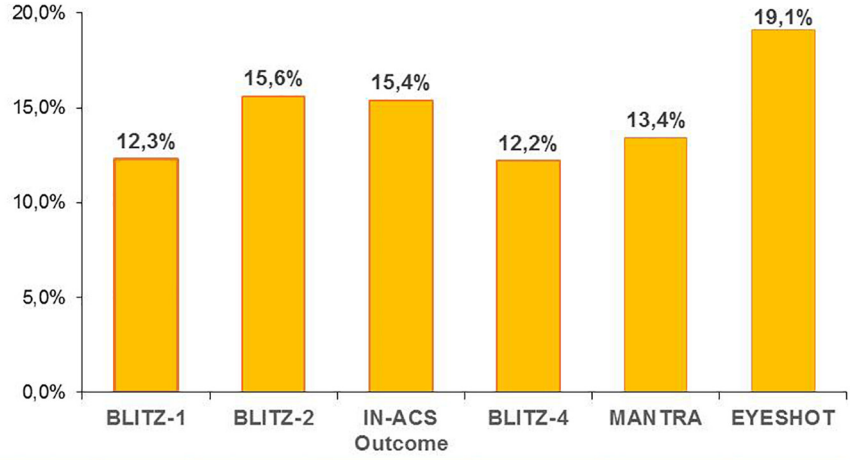
The overall prevalence of PAD did not change significantly over time in the six surveys (p for trend = 0.16).

During the observation period, the rates of patients with high risk features increased, particularly with regard to chronic kidney disease (+200%) and prior coronary revascularization (+160%) (Table 2). On the other hand, indicators of a more careful medical prevention, such as less active smoking and less prior stroke, significantly increased. The use of antithrombotic therapies during hospital stay, including antiplatelet agents and heparins, increased over time in patients with PAD, with the only exception of oral anticoagulation therapy (Table 2).

3.3. Coronary angiography and revascularization

As shown in Fig. 2, the rates of coronary angiography and percutaneous coronary intervention (PCI) significantly increased over the years both in patients with and without PAD (all p for trend values $<$ 0.0001). However, rates of coronary angiography (72.0% vs 79.2%, $p < 0.0001$) and PCI (42.9% vs 51.8%, $p < 0.0001$), remained significantly lower in patients with PAD, as compared to those without PAD.

The median time from hospital admission to coronary angiography



Year	2001	2003	2006-2007	2009-2010	2009-2010	2013-2014
Centres	296	275	38	163	52	203
Total n. of NSTE-ACS pts	585	1059	3519	5786	3479	1439

Fig. 1. - Incidence of PAD among patients with an initial diagnosis of NSTE-ACS enrolled in different registries.

Table 1
Clinical characteristics, hemodynamic parameters and pharmacological therapies of NSTE-ACS patients according to the presence of PAD.

	No PAD n = 13,641	PAD n = 2226	p value
Age, yrs. (mean ± SD)	68 ± 13	75 ± 9	< 0.0001
Females, n (%)	4470 (32.8)	650 (29.2)	0.0008
Active smokers, n (%)	3651 (26.8)	434 (19.5)	< 0.0001
Diabetes mellitus, n (%)	3698 (27.1)	1030 (46.3)	< 0.0001
Hypertension, n (%)	8385 (61.5)	1748 (78.5)	< 0.0001
Chronic kidney disease, n (%)	1132 (8.3)	642 (28.8)	< 0.0001
Previous stroke/TIA, n (%)	739 (5.4)	353 (15.9)	< 0.0001
History of HF, n (%)	537 (3.9)	251 (11.3)	< 0.0001
History of angina, n (%)	2533 (18.6)	735 (33.0)	< 0.0001
Previous MI, n (%)	2784 (20.4)	789 (35.4)	< 0.0001
Previous PCI/CABG, n (%)	2870 (21.0)	834 (37.5)	< 0.0001
Variables at CCU admission			
Killip IV, n (%)	140 (1.0)	64 (2.9)	< 0.0001
Atrial fibrillation, n (%)	975 (7.2)	228 (10.2)	< 0.0001
SBP, mmHg (mean ± SD)	141 ± 25	142 ± 28	0.03
HR, bpm (mean ± SD)	79 ± 19	82 ± 21	< 0.0001
LVEF, % (mean ± SD)	51 ± 10	48 ± 11	< 0.0001
Antithrombotic drugs during hospital stay, n (%)			
Aspirin	12,792 (93.8)	1995 (89.6)	< 0.0001
GPI	3221 (23.6)	420 (18.9)	< 0.0001
Dual antiplatelet therapy	10,809 (79.2)	1642 (73.8)	< 0.0001
Oral anticoagulant therapy	219 (2.6)	83 (5.5)	< 0.0001
Unfractioned heparin	5758 (42.2)	896 (40.3)	0.08
LMWH	7084 (51.9)	1156 (51.9)	1.0

GPI: glycoprotein IIb/IIIa inhibitors; HF: heart failure; HR: heart rate; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NSTE-ACS: Non-ST elevation acute coronary syndrome; SBP: systolic blood pressure; HR: heart rate; TIA: transient ischemic attack.

significantly decreased from 119.2 [inter-quartile range (IQR): 46.7–204.4] hours in 2001 to 31.0 (IQR: 14.1–68.0) hours in 2014 (p for trend < 0.0001) in patients with PAD and from 111.8 (IQR: 46.0–184.2) hours in 2001 to 22.2 (IQR: 8.2–47.8) hours in 2014 in patients without PAD (p for trend < 0.0001).

A multivessel coronary artery disease (CAD), defined as significant stenoses in ≥2 coronary arteries, was present in 70.1% of patients with PAD and in 50.5% of patients without PAD undergoing coronary angiography (p ≤0.0001). The presence of multivessel CAD did not change over time among patients with PAD, while it significantly decreased in those without PAD (p for trend = 0.005). On the other hand, absence of significant coronary angiographic stenoses was observed in 6.4% of patients with PAD and in 10.9% of patients without PAD (p ≤ 0.0001), without significant time trends for both groups.

3.4. In-hospital outcome

As shown in Table 3, as compared to patients without PAD, crude in-hospital mortality was at least two times higher among patients with PAD. However, in-hospital mortality did not change significantly over time, irrespective of PAD status. Adding to PAD two, three or more conventional risk factors such as age ≥ 75 years, chronic kidney disease, diabetes mellitus and prior MI, the overall risk of in-hospital mortality increased (Fig. 3), without significant time trends.

The rates of re-MI, and major bleeding were two-fold higher in patients with PAD compared to those without PAD, without significant change over time in both groups (Table 3).

At multivariable analysis in the whole NSTE-ACS population, the adjusted risk of death was significantly lower in subsequent years, as compared to 2001. A history of PAD was found to be an independent predictor of in-hospital death (OR: 1.75; 95% CI: 1.35–2.27; p < 0.0001) together with other well known predictors, such as hemodynamic parameters on admission, diabetes mellitus, renal dysfunction and history of cerebrovascular events (Fig. 4).

4. Discussion

The present analysis of six consecutive, nationwide, prospective registries covering 14 years of observation shows that: 1. PAD at admission is present in nearly 15% of the NSTE-ACS cases admitted to CCUs; 2. As compared to patients without PAD, those with PAD are older and have significantly worse clinical characteristics, both as prior cardiovascular history and as clinical presentation, and these high-risk characteristics and comorbidities have increased over the observation period; 3. The use of coronary angiography and PCI in the acute phase has dramatically increased in NSTE-ACS patients with PAD over the years; 4. Whereas crude in-hospital mortality did not change over time, we observed a significant reduction in comorbidity-adjusted mortality as compared to 2001, and patients with PAD persistently presented an event rate at least twice as high compared to patients without PAD.

Table 2
Baseline characteristics of NSTE-ACS patients with PAD from 2001 to 2014.

	BLITZ-1 (n = 72)	BLITZ-2 (n = 165)	In-ACS Outcome (n = 541)	BLITZ-4 (n = 708)	MANTRA (n = 465)	EYESHOT (n = 275)	p for trend
Age, yrs. (mean ± SD)	74 ± 9	74 ± 10	74 ± 9	75 ± 8	74 ± 9	76 ± 9	0.02
Females, n (%)	19 (26.4)	53 (32.1)	158 (29.2)	200 (28.3)	133 (28.6)	87 (31.6)	0.79
Active smokers, n (%)	17 (23.6)	43 (26.1)	106 (19.6)	132 (18.6)	102 (21.9)	34 (12.4)	0.01
Diabetes mellitus, n (%)	30 (41.7)	69 (41.8)	228 (42.1)	359 (50.7)	223 (48.0)	121 (44.0)	0.15
Hypertension, n (%)	50 (69.4)	117 (70.9)	416 (76.9)	562 (79.4)	372 (80.0)	231 (84.0)	0.0002
CKD, n (%)	10 (13.9)	32 (19.4)	145 (26.8)	227 (32.1)	112 (24.1)	116 (42.2)	< 0.0001
Previous stroke/TIA, n (%)	19 (26.4)	46 (27.9)	99 (18.3)	71 (10.0)	67 (14.4)	51 (18.6)	0.002
History of HF, n (%)	13 (18.1)	22 (13.3)	52 (9.6)	66 (9.3)	51 (11.0)	47 (17.1)	0.33
History of angina, n (%)	36 (50.0)	45 (27.3)	201 (37.2)	251 (35.5)	116 (25.0)	86 (31.3)	0.002
Previous MI, n (%)	34 (47.2)	59 (35.8)	221 (39.0)	204 (28.8)	166 (35.7)	115 (41.8)	0.73
Previous PCI/CABG, n (%)	13 (18.1)	31 (18.8)	198 (36.6)	282 (39.8)	180 (38.7)	130 (47.3)	< 0.0001
Variables at CCU admission							
Killip IV, n (%)	1 (1.4)	4 (2.4)	7 (1.3)	19 (2.7)	21 (4.5)	12 (4.4)	0.003
Atrial fibrillation, n (%)	5 (6.9)	21 (12.7)	55 (10.2)	66 (9.3)	45 (9.7)	36 (13.1)	0.48
SBP, mmHg (mean ± SD)	142 ± 29	146 ± 29	143 ± 28	140 ± 27	143 ± 30	141 ± 26	0.41
HR, bpm (mean ± SD)	86 ± 21	84 ± 23	81 ± 20	81 ± 20	85 ± 23	81 ± 22	0.78
LVEF, % (mean ± SD)	52 ± 12	48 ± 10	49 ± 11	47 ± 11	49 ± 11	47 ± 11	0.18
Antithrombotic drugs during hospital stay, n (%)							
Aspirin	56 (77.8)	134 (81.2)	487 (90.0)	635 (89.7)	442 (95.1)	241 (87.6)	0.0002
GPI	15 (20.8)	37 (22.4)	118 (21.8)	135 (19.1)	101 (21.7)	14 (5.1)	< 0.0001
Dual antiplatelet therapy	17 (23.6)	66 (40.0)	389 (71.9)	547 (77.3)	403 (86.7)	220 (80.0)	< 0.0001
Oral anticoagulant therapy	4 (5.6)	12 (7.3)	26 (4.8)	26 (5.6)	N/A	15 (5.5)	0.88
Unfractioned heparin	38 (52.8)	69 (41.8)	169 (31.2)	285 (40.3)	179 (38.5)	156 (56.7)	0.0005
LMWH	41 (56.9)	113 (68.5)	357 (66.0)	336 (47.5)	188 (40.4)	121 (44.0)	< 0.0001

CKD: chronic kidney disease; GPI: glycoprotein IIb/IIIa inhibitors; HF: heart failure, HR: heart rate; LMWH: low-molecular weight heparins; LVEF: left ventricular ejection fraction; MI: myocardial infarction; NSTEACS: Non-ST elevation acute coronary syndrome; SBP: systolic blood pressure; HR: heart rate; TIA: transient ischemic attack.

Indeed, at multivariable analysis, PAD resulted to be an independent predictor of in-hospital mortality among NSTE-ACS patients.

The prevalence of PAD in the ACS population varies from 5 to 20%, depending on definition of PAD, patient selection and observation period [1–6,15]. Because of a growing proportion of older patients, the prevalence of NSTE-ACS patients with PAD is expected to rise [15]. In addition, patients with PAD present a higher prevalence of several ischemic risk factors, such as diabetes mellitus, hypertension, prior MI, prior revascularization and chronic renal insufficiency compared to patients without PAD [16–18]. Our study confirms these findings and shows that, over time, PAD patients with increasing clinical complexity and high-risk characteristics have been admitted and treated invasively in the italian CCU network, even if the absolute rate of in-hospital invasive procedures resulted persistently lower compared to patients without PAD.

Although guidelines recommend an early invasive approach to treat the high-risk NSTE-ACS populations, and some post-hoc analyses of randomized clinical trials showed that an early invasive management is beneficial in terms of morbidity and mortality in ACS patients with PAD [13,19], these patients are usually undertreated in the real-world setting. The observed lower rates of coronary angiography might be related to advanced age and the higher burden of comorbidities often associated with PAD, whereas the lower rate of revascularization might reflect the fact that patients with PAD have usually a more diffuse and

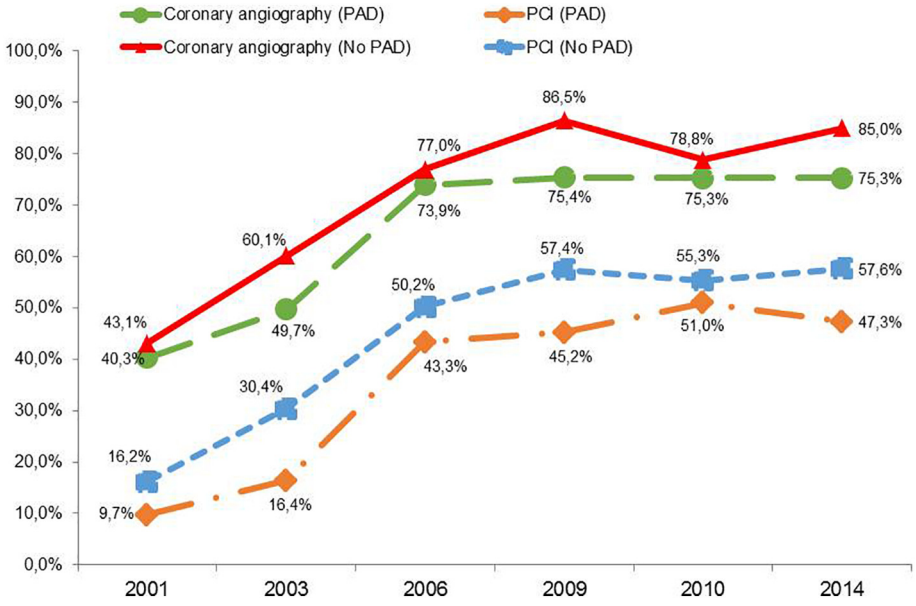


Fig. 2. - In-hospital rates of coronary angiography and percutaneous coronary intervention (PCI) in NSTE-ACS patients with or without PAD over time.

Table 3
In-Hospital major clinical events of NSTE-ACS patients with and without PAD.

		BLITZ-1 (PAD, n = 72; no PAD, n = 513)	BLITZ-2 (PAD, n = 165; no PAD, n = 894)	In-ACS Outcome (PAD, n = 541; no PAD, n = 2978)	BLITZ-4 (PAD, n = 708; no PAD, n = 5078)	MANTRA (PAD, n = 465; no PAD, n = 3014)	EYESHOT (PAD, n = 275; no PAD, n = 1164)	p for trend
Death	PAD, n (%)	10 (13.9)	5 (3.0)	22 (4.1)	33 (4.7)	28 (6.0)	10 (3.6)	0.40
	No PAD, n (%)	20 (3.9)	12 (1.3)	33 (1.1)	88 (1.7)	58 (1.9)	23 (2.0)	0.84
Re-MI	PAD, n (%)	4 (5.6)	0 (0.0)	15 (2.8)	12 (1.7)	12 (2.6)	4 (1.5)	0.51
	No PAD, n (%)	13 (2.5)	4 (0.5)	53 (1.8)	44 (0.9)	57 (1.9)	11 (1.0)	0.60
Stroke	PAD, n (%)	1 (1.4)	1 (0.6)	3 (0.6)	7 (1.0)	5 (1.1)	0 (0.0)	0.63
	No PAD, n (%)	5 (1.0)	2 (0.2)	9 (0.3)	26 (0.5)	15 (0.5)	3 (0.3)	0.76
Major bleeding	PAD, n (%)	2 (2.8)	6 (3.6)	6 (1.1)	27 (3.8)	15 (3.2)	5 (1.8)	0.76
	No PAD, n (%)	5 (1.0)	7 (0.8)	12 (0.4)	87 (1.7)	24 (0.8)	15 (1.3)	0.10

MI: myocardial infarction.

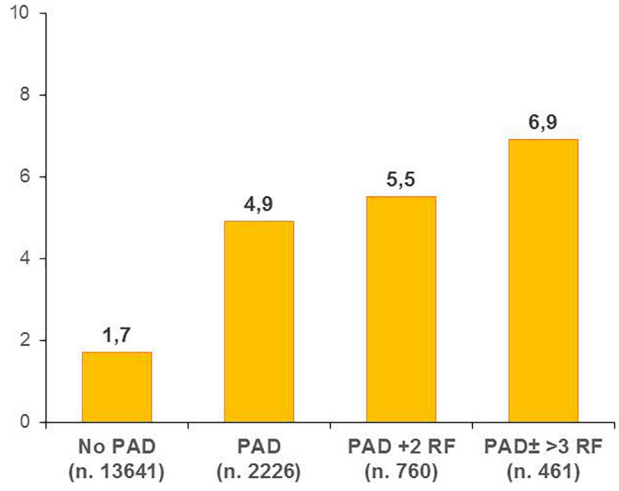


Fig. 3. - Overall in-hospital mortality rate among NSTE-ACS patients without PAD, with PAD alone and with PAD in addition to 2 or ≥ 3 conventional cardiovascular risk factors (i.e. age ≥ 75 years, chronic kidney disease, diabetes mellitus and prior myocardial infarction).

severe coronary atherosclerosis, together with an impaired arterial remodeling and greater disease progression compared to patients without PAD [1,5,6,20,21], as also confirmed in our series. Our time trends demonstrate that patients with PAD have been treated more aggressively in terms of invasive procedures and antithrombotic therapies, suggesting that physicians' awareness on the prognostic impact of PAD in ACS increased over time.

Several international registries [4,22,23] showed patients with PAD present higher short-term mortality rates compared to patients without PAD. Similarly, analyses from clinical trial databases have demonstrated an increased risk of short-term ischemic outcomes among patients with NSTE-ACS and PAD, including those receiving an early and effective coronary revascularization [2,24,25]. In our study, over the 14 years of observation, NSTE-ACS patients with PAD constantly presented higher in-hospital mortality compared to patients without PAD. In addition, PAD resulted as a strong independent predictor of mortality at multivariable analysis, confirming PAD a marker of risk among patients presenting with NSTE-ACS and supporting the need for intensive secondary preventive measures in this high-risk subgroup of patients [26]. In this regard, recent studies demonstrated a survival benefit of novel antithrombotic strategies in patients with PAD and concomitant CAD [27–30].

5. Limitations

There are some limitations to our analysis. First, we could not confirm diagnosis of PAD with repeat noninvasive testing. In addition, PAD was recorded by investigators based on clinical history and established clinical diagnosis, at the time of enrolment. As a result, it is possible that additional patients with asymptomatic PAD may have been missed. This limitation does not diminish the importance of the current observation on the impact of PAD on in-hospital outcome, since it has been demonstrated that ACS patients with clinical PAD have higher rates of major cardiovascular events than patients with subclinical PAD [22].

Moreover, some registries (BLITZ and EYESHOT) included the majority of italian CCUs, whereas others (IN-ACS Outcome and MANTRA) included selected sites, even if well representative of Italian cardiology centers in terms of geographical distribution and level of complexity. When the temporal trend is evaluated, this inconsistency may skew results.

Finally, our analysis is limited to hospital stay since no follow-up data are available for the majority of the surveys. It is well known that

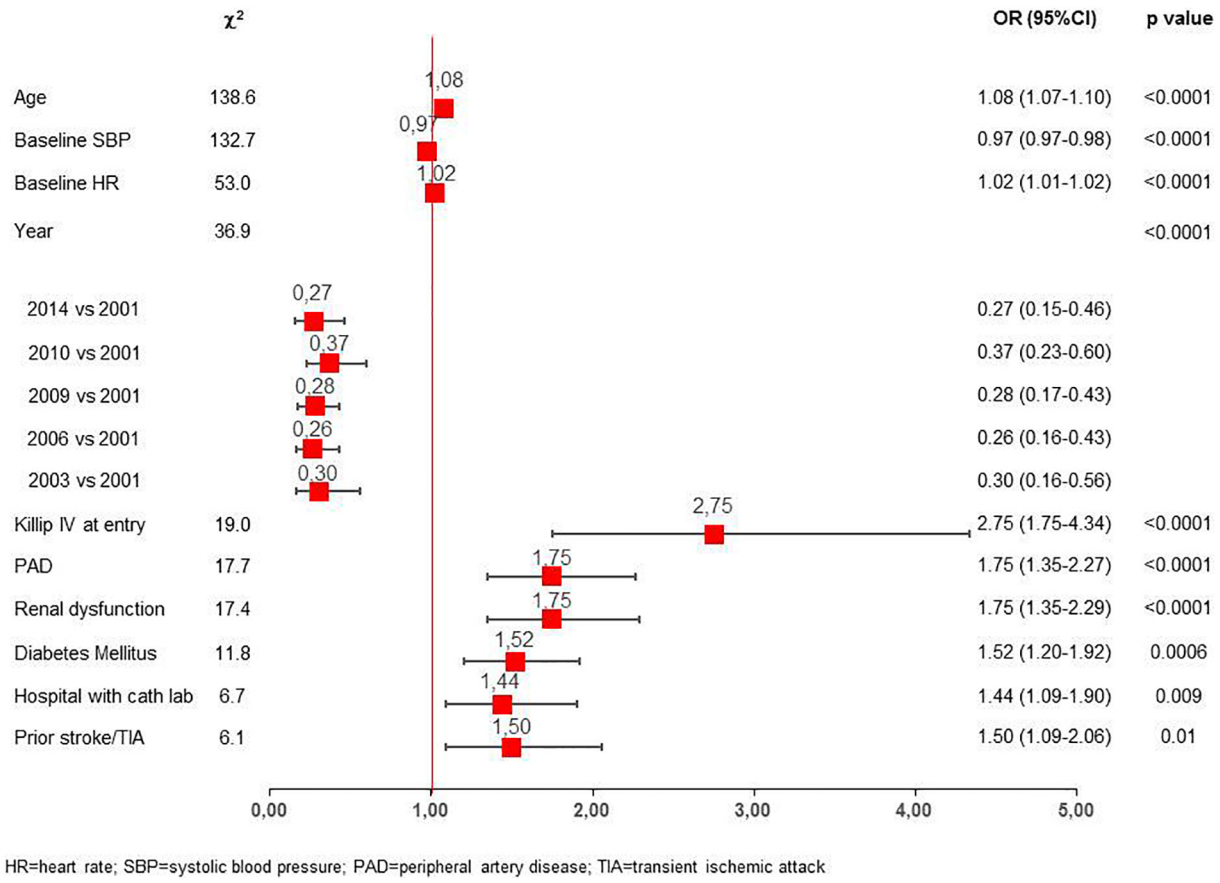


Fig. 4. - Multivariable logistic regression analysis on in-hospital mortality over time in the overall population with NSTE-ACS.
Abbreviations. CI: confidence interval; HR; heart rate; MI: myocardial infarction; OR: odds ratio; PCI: percutaneous coronary intervention; SBP: systolic blood pressure; TIA: transient ischemic attack.

in-hospital outcome may be relatively uneventful even in the high-risk patients with NSTE-ACS and that any benefit of an invasive approach and secondary prevention strategies becomes apparent only after a few months of follow-up [31,32]. However, the present data that the high-risk category of PAD patients has received an almost systematic invasive approach on a national basis, without paying the price of in-hospital adverse events, particularly bleeding and stroke, represents an important observation in terms of quality of care.

6. Conclusions

Patients with PAD represent a high-risk subgroup within the NSTE-ACS population, due to older age, a higher burden of comorbidities, and more severe CAD. Over the 14 years of observation, despite worsening baseline characteristics, there has been an almost systematic shift from a conservative to an invasive approach using early coronary angiography and revascularization.

Longer follow-up data will have to determine the impact of invasive approach as well as secondary preventive measures on long term outcomes in this high risk population.

Conflicts of interest

Dr. De Luca reports personal fees from Astra Zeneca, Bayer, Boehringer-Ingelheim, Eli Lilly, Daiichi Sankyo, Menarini and The Medicines Company, outside the submitted work; Dr. Di Pasquale reports grants and personal fees from Boheringer Ingelheim, Bayer, Pfizer, and Daiichi Sankyo, outside the submitted work; Dr. Gonzini, employer of Heart Care Foundation which conducted the studies, reports Institutional grants from GlaxoSmithKline, Italy, grants from Merck, Sharp&Dohme, Italy, outside the submitted work; Dr. De Servi reports personal fees from Astra Zeneca, Eli Lilly, Daiichi Sankyo and The Medicines Company, outside the submitted work; Dr. Di Lenarda reports personal fees from Astra Zeneca, Bayer, Pfizer, BMS, Boehringer-Ingelheim, Daiichi Sankyo, Novartis, Merck Sharp&Dohme, Menarini; Dr. Savonitto reports grants and personal fees from Eli Lilly, Novartis, Iroko, Daiichi Sankyo and Pfizer, outside the submitted work; Dr. Bolognese reports personal fees from Astra Zeneca and Daichi Sankyo, outside the submitted work; the other authors have nothing to disclose.

Author Contributions

Each author contributed significantly to the submitted work. In particular, LDL, SS and LB drafted the manuscript; GDP, ADC, FC, AB, GC, SDS, ZO, MMG and ADL revised it critically; LG analyzed the data.

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