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Clinical research

Epidemiology of non-ST elevation acute coronary syndromes in the Italian cardiology network: the BLITZ-2 study

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Aims Acute coronary syndromes without ST-segment elevation (NSTEACS) represent an increasingly frequent cause of hospital admission. The BLITZ-2 study was planned to survey the epidemiology and management strategies of NSTEACS in the Italian cardiological network.

Methods and results The study included 1888 patients with NSTEACS in 275 hospitals in 3 weeks. At admission, almost 20% of patients showed clinical signs of heart failure, half showed ST-segment depression, and half showed any positive biochemical myocardial necrosis marker. Patients admitted to hospitals without CathLab ($n = 973$) were older ($P = 0.0005$) and with higher Killip class on admission ($P < 0.0001$) when compared with those admitted to hospitals with CathLab ($n = 915$). During index hospitalization, 76% of the patients initially admitted to hospitals with invasive capability underwent coronary angiography and 39% percutaneous coronary intervention when compared with 39 and 17.2% of those admitted to hospitals without CathLab ($P < 0.001$). Overall, 30-day mortality was 2.4% (2.0% in patients with invasive capability vs. 2.9% in hospitals without CathLab, $P = 0.2$). Cardiac ischaemic events at 30 days (recurrent MI, recurrent angina, and re-hospitalization for ACS) were significantly higher in the group of patients admitted to hospitals without CathLab (OR 1.71, 95% CI 1.24–2.35). However, after multivariable adjustment, only advanced age (OR 1.043, 95% CI 1.021–1.065, $P < 0.0001$) and Killip class >1 (OR 1.633, 95% CI 1.020–2.614, $P = 0.04$) resulted in independent predictors of death, in-hospital MI, and re-admission for ACS, whereas the absence of an on-site CathLab did not predict an adverse outcome (OR 1.104, 95% CI 0.734–1.660).

Conclusion According to this, the nationwide registry outcome is only marginally influenced by invasive procedures. Contemporary management of patients with NSTEACS in Italy is primarily driven by resource availability.

Introduction

Acute coronary syndromes without ST-segment elevation (NSTEACS) represent an increasingly frequent cause of hospital admission, as it is the most frequent presentation of coronary instability in elderly patients and in those with prior cardiac events or coronary revascularizations. Experimental data from randomized clinical trials have clearly shown the efficacy of an aggressive pharmacological and interventional approach[1–3] in this patient subset, particularly in high-risk patients. On the basis of this evidence, practice guidelines on NSTEACS recommend an early, risk-tailored, invasive strategy, including aggressive antithrombotic therapy, coronary angiography, and, possibly, revascularization.[4,5] However, the extent to which this approach is being applied in clinical practice is still unclear. Also, the availability of these treatments made costs enormously high, without so far proving to be effective in the real scenario.[6,7] The BLITZ-2 study was planned to survey the epidemiology and management strategies of NSTEACS in the Italian cardiological network. This study was part of a comprehensive effort[8] to update

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knowledge of the epidemiology, organization-related factors, therapeutic management, and outcome of ACS in order to establish new health-care policy programmes.

Methods

Study organization

The study was designed by the Italian Hospital Cardiology Association (ANMCO) as a nationwide survey on patients admitted to the Cardiology Departments (including coronary care units, step-down units, and cardiological wards) for NSTEACS. Out of all the Italian cardiology wards invited ($n = 625$), 275 (44%) participated in the study, with a homogeneous distribution throughout the country. The enrolling period was 22 days, between the 6th and the 27th of May 2003. A summary of hospital characteristics is given in *Table 1*.

Patients

Each centre agreed to enrol all of the patients consecutively admitted within 24 h from the latest symptomatic episode of an acute coronary syndrome (or within 48 h in the case of subsequent transfer to cardiology). The diagnosis of NSTEACS could be made either on admission or later during the hospital stay and had to be confirmed either by ischaemic ECG changes (ST-depression of >0.5 mm, negative T-wave >1 mm, and transient ST-elevation lasting <20 min) or by a typical release of myocardial necrosis biochemical markers, such as troponins, CK-MB, or total CK. Of the biochemical markers, the CRF collected reference values, the baseline and peak values relative to the index episode, as well as those associated with any further ischaemic episodes, and percutaneous coronary interventions (PCIs). Exclusion criteria were undetermined ECG (paced rhythm or left bundle branch block), persistent ST-segment elevation, secondary acute coronary syndromes (e.g. post-surgery, anaemia, or thyreotossicosis-induced), and NSTE myocardial infarction, following coronary intervention procedures. Signed informed consent was obtained from the patients at enrolment.

Data collection

Data collection was completely paperless, using a web-based CRF. This allowed us to add on-screen definitions and suggestions, checks for mandatory variables, and data range and logical consistency for almost all variables.

Thirty-day follow-up

The 30-day follow-up was conducted by hospital visits and concerned major cardiac events occurred from hospital discharge, including new hospitalizations for unstable angina and myocardial infarction, heart failure, stroke, and revascularization procedures.

Table 1 Characterization of participating hospitals

Type of hospital	*n*	%
Without CCU	15	5.6
CCU only	142	53.2
CCU, CathLab (no interventional)	28	10.5
CCU, interventional CathLab	33	12.4
CCU, interventional CathLab, cardiac surgery	49	18.3

n, number of Centers; CCU, coronary care unit; CathLab, Catheterization Laboratory.

Definitions

Myocardial necrosis was defined when the serum CK-MB or troponin value was greater than the upper reference limit defined for each biochemical marker at each centre, according to the ESC/ACC definition.[9] Clinical re-infarction during initial hospitalization was diagnosed in the presence of new ischaemic symptoms and a re-elevation of biochemical myocardial necrosis markers with or without concurrent ECG changes. After the index episode, new ischaemic events (ECG changes were mandatory) were defined as recurrent when occurring despite optimal medical therapy and as refractory when they mandated coronary angiography within 24 h. Coronary-intervention-related infarction was defined according to the ACC/AHA guidelines.[10]

Bleeding was defined major when it was intracranial, retroperitoneal, intraocular, with any haemoglobin loss >5 g/dL (or haematocrit reduction ≥15%), or when it required transfusion. Any other bleeding was defined minor.

As far as treatment strategies were concerned, patients were grouped as having had an invasive strategy when they had undergone coronary angiography/PCI or coronary artery bypass graft (CABG) during index hospital admission without a preliminary functional evaluation (exercise stress test, dobutamine or dypiridamole stress echocardiography, or myocardial perfusion scintigraphy). All the remaining patients were considered as having been treated according to a conservative strategy.

Hospitals were categorized according to the presence of a catheterization laboratory (either 'hospital with CathLab', or 'hospital without CathLab'), irrespective of the interventional capabilities.

Statistical analysis

Categorical variables are presented as frequencies and percentages and compared by the χ^2 test. Time intervals are presented as either mean (and standard deviation) or median times (and inter-quartile ranges, IQRs). Other continuous variables are presented as mean and standard deviation and compared by the *t*-test or the Mann–Whitney *U* test for comparison of two groups. No adjustments were made for multiple testing and interpretation of the results should be made accordingly.

Multivariable analysis (logistic model) was used to evaluate: (i) the independent predictors of an invasive strategy and (ii) the independent predictors of the combined endpoint of death, in-hospital myocardial infarction, and re-admission for ACS. The following variables, which were considered potential predictors of study endpoints on the base of clinical judgement and literature data, were inserted in the models: type of hospital (without CathLab vs. with CathLab), age (as continuous), heart rate (as continuous), systolic blood pressure (as continuous), gender (female vs. male), history of diabetes (yes vs. no), biochemical necrosis marker (positive, negative, unknown, and reference negative), Killip class at entry (>1 vs. 1), family history of ischaemic heart disease (yes vs. no), and ST-segment depression (yes vs. no). The linearity of the continuous variables was tested using the Box–Tidwell transformation. A *P*-value <0.05 was considered to represent a statistically significant difference. All tests were two-sided. All analyses were performed with SAS system software (SAS Institute Inc., Cary, NC, USA).

Results

Population

Between 6 and 27 May 2003, the 275 participating centres enrolled 1888 consecutive patients (median six patients per centre, IQR 3–10). The demographic characteristics and the clinical history of the population are shown in *Table 2*. The data are presented both for the overall population and according to the presence or absence of a

Table 2 Population demographics and clinical history

	All $n = 1888$	Hospitals without CathLab $n = 915$ (48%)	Hospitals with CathLab $n = 973$ (52%)	P^{a}
Men (%)	1282 (67.9)	596 (65.1)	686 (70.5)	0.0125
Age (years) (mean ± SD)	68 ± 12	69 ± 12	67 ± 12	0.0005
Age (min–max)	25–98	25–95	31–98	
Age >74 years (%)	605 (32.0)	331 (36.2)	274 (28.2)	0.0002
Risk factors				
Family history for IHD (%)	603 (31.9)	276 (30.2)	327 (33.6)	0.11
Active cigarette smoking (%)	550 (29.1)	245 (26.8)	305 (31.4)	0.033
Dislipidaemia (%)	880 (46.6)	412 (45.0)	468 (48.1)	0.18
Diabetes (%)	515 (27.3)	268 (29.3)	247 (25.4)	0.06
Systemic hypertension (%)	1220 (64.6)	589 (64.4)	631 (64.9)	0.83
Stroke/TIA (%)	172 (9.1)	90 (9.8)	82 (8.4)	0.29
Peripheral vasculopathy (%)	303 (16.1)	156 (17.1)	147 (15.1)	0.25
Renal insufficiency (s. creatinine >2 mg/dl) (%)	119 (6.3)	59 (6.5)	60 (6.2)	0.80
Severe neoplastic disease (%)	59 (3.1)	28 (3.1)	31 (3.2)	0.88
Recent haemorrhagic events (%)	20 (1.1)	9 (1.0)	11 (1.1)	0.76
History of cardiac disease (%)	879 (46.6)	437 (47.8)	442 (45.5)	0.31
Known coronary disease (%)	506 (26.8)	218 (23.8)	288 (29.6)	0.0046
Duration of IHD (years) (mean ± SD)[b] IQR	6.8 ± 6.8 1/5/10	6.9 ± 6.7 1/5/11	6.6 ± 6.9 1/5/10	0.39
Chronic angina (%)	382 (20.2)	207 (22.6)	175 (18.0)	0.0122
Prior myocardial infarction (%)	591 (31.3)	288 (31.5)	303 (31.1)	0.88
Any prior revascularization (%)	365 (19.3)	151 (16.5)	214 (22.0)	0.003
Prior PCI (%)	260 (13.8)	106 (11.6)	154 (15.8)	0.008
Prior CABG (%)	158 (8.4)	70 (7.7)	88 (9.0)	0.27
Heart failure (%)	115 (6.1)	62 (6.8)	53 (5.5)	0.23

[a]Not adjusted for multiple comparisons.
[b]Data known for 764 patients (375 patients in hospital without CathLab, 389 in hospital with CathLab).

catheterization laboratory in the enrolling hospital. Patients admitted to the hospitals with CathLab were younger and more likely to have had documented coronary disease and prior myocardial revascularizations.

The patients' risk profiles were classified according to clinical variables, ECG, biochemical markers, and the TIMI risk score for NSTEACS[10] (*Table 3*). Overall, the enrolled population was at moderate-tohigh-risk. At admission, almost 20% of patients showed pulmonary signs of heart failure, half showed ST-segment depression, and 51% had elevated levels of any biochemical myocardial necrosis marker (this latter proportion increased to 75% during hospital stay). Troponins T or I were assayed in 90% of the patients. Only 13% of the patients had a low TIMI risk score. Hospitals with CathLab admitted significantly fewer patients with heart failure and atrial fibrillation, though with comparable ECG and biochemical-marker profile.

Risk stratification and therapeutic approach

Tests for residual inducible ischaemia (exercise stress, stress echocardiography, or myocardial perfusion scintigraphy) were conducted in ~14% of the cases, more frequently in hospitals without CathLab, in younger patients (16% in patients <55 years, 12% in those 55–74 years, 5.1% in those >74 years, $P < 0.0001$), and in those with lower TIMI risk class (24% TIMI 1–2, 10% TIMI 3–4, 6.3% TIMI 5–7, $P < 0.0001$).

During index admission, coronary angiograms, PCI, and CABG were performed twice as often in hospitals with CathLab when compared with other hospitals. Despite a catch-up during follow-up, by day 30, patients initially admitted to hospitals without CathLab received 33% fewer coronary angiograms, 40% fewer PCIs, and 27% fewer CABGs. At 30 days, 66% of the patients who had undergone coronary angiograms had also undergone myocardial revascularization, with a PCI-to-CABG ratio of 3:1 (*Table 4*).

The median delay to coronary angiography during the index admission was 58 h (IQR 25–109) in hospitals with CathLab and 96 h (IQR 49–150) in those without CathLab ($P < 0.0001$). The median delay to bypass surgery was 175 h (IQR 107–277) in hospitals with CathLab and 174 h (IQR 120–258) in those without CathLab ($P = 0.82$).

According to the study definition, 843 patients (45%) were treated conservatively, whereas 1039 (55%) according to an invasive approach. The presence of high-risk characteristics, singularly (elevated biochemical markers) or clustered (elevated biochemical markers and ST-segment depression) did not prompt more often an aggressive strategy (*Table 5*). Other high-risk subgroups, such as the elderly, those with heart failure or TIMI class 5–7, diabetics, and those with both ST-segment depression, positive marker, and diabetes, were managed more often conservatively.

The type of strategy was influenced by the presence of a CathLab on-site. In hospitals with an on-site CathLab, an invasive strategy was adopted in 74% of the patients and a conservative strategy in 26%. In hospitals without CathLab, the corresponding figures were 36 and 64%, respectively. However, in both type of hospitals the use of an invasive strategy was not more frequent in high and very high-risk

Table 3 Patient risk profile

	All $n = 1888$	Hospitals without CathLab $n = 915$	Hospitals with CathLab $n = 973$	P[a]
TIMI RISK SCORE (%)				0.69
1–2	251 (13.3)	126 (13.8)	125 (12.8)	
3–4	951 (50.4)	452 (49.4)	499 (51.3)	
5–7	686 (36.3)	337 (36.8)	349 (35.9)	
Systolic blood pressure <100 mmHg (%)	46 (2.4)	26 (2.8)	20 (2.1)	0.27
Heart rate >100 bpm (%)	215 (11.4)	124 (13.6)	91 (9.4)	0.0041
Killip Class >1 (%)	367 (19.4)	213 (23.3)	154 (15.8)	<0.0001
Myocardial necrosis marker				
Assayed (%)	1851 (98.0)	906 (99.0)	945 (97.1)	0.005
Positive during hospital stay (%)	1387 (74.9)	666 (73.5)	721 (76.3)	0.17
Positive at admission (%)	942 (50.9)	425 (46.9)	517 (54.7)	0.0008
ECG				
Normal (%)	275 (14.6)	138 (15.1)	137 (14.1)	0.16
ST-elevation (transient) (%)	144 (7.6)	62 (6.8)	82 (8.4)	
ST-depression (%)	934 (49.5)	471 (51.5)	463 (47.6)	
T wave negative (%)	535 (28.3)	244 (26.6)	291 (29.9)	
Atrial fibrillation/flutter (%)	142 (7.5)	87 (9.5)	55 (5.7)	0.002

[a]Not adjusted for multiple comparisons.

patients (*Table 6*). The vast majority of patients with heart failure (74%), ST-segment depression (67%), positive biochemical marker (65%), or diabetes (70%) admitted to hospitals without CathLab did not undergo coronary angiography. In hospitals with CathLab, an invasive strategy was used much more extensively; however, high-risk subgroups were equally less likely to receive an aggressive approach. In both hospital types, the TIMI risk score did not affect the likelihood of an invasive strategy.

Predictors of invasive strategy

At logistic regression analysis, the presence of an on-site CathLab, younger age, Killip class 1 at entry and low heart rate on admission were predictors of an invasive strategy (*Table 7*). Gender, diabetic status, history of ischaemic heart disease, systolic blood pressure on admission, ST-segment depression, and a positive necrosis marker were not independently associated with an invasive strategy.

Use of hospital network

Of the entire study population, 462 patients (25%) were transferred from the first admission hospital in order to undergo coronary angiography. In contrast, of the 973 patients admitted to centres with a CathLab, 108 (11%) underwent coronary angiography coming from a hospital without CathLab. Out of all patients enrolled in hospitals without CathLab, 354 (39%) underwent coronary angiography, 157 (17%) PCI, and 34 (3.7%) CABG. When compared with patients managed conservatively, those transferred for invasive procedures were more often at intermediate TIMI risk score (54 vs. 47%) and less often at higher risk (33 vs. 39%). A similar TIMI risk score distribution related to the type of strategy was observed in centres with CathLab (*Figure 1*).

Hospital course and 30-day follow-up

An uncomplicated clinical course was significantly more frequent in patients treated in hospitals with CathLab, with fewer ischaemic recurrences (−3.7%, $P = 0.003$) and less heart failure, arrhythmias, bleeding, or stroke (−3.1%, $P = 0.014$) (*Table 8*).

Overall, marked differences were present in re-infarction rate according to its definition. When physician-defined cases (19 patients, 1.0%) were merged to the cases adjudicated based on the levels of the biochemical markers, the overall incidence was of 46 re-infarctions (2.4%). Similarly, periprocedural re-infarctions increased from eight cases (0.4%) to 67 cases (3.5%).

The duration of hospital course was on average 8.8 ± 4.6 days (of which 3.9 ± 2.5 nights were spent in CCU), with a median value of 8 days (IQR 6–10). A complicated course resulted in 1-day longer stay (9.8 ± 6.0 vs. 8.6 ± 4.3, $P = 0.0132$). Patients treated with coronary angioplasty stayed in-hospital 7.7 ± 3.4 days when compared with 9.2 ± 4.9 days for patients who did not ($P < 0.0001$), but no differences in the overall length of stay were observed between hospitals with or without CathLab (8.9 ± 4.9 vs. 8.7 ± 4.2, $P = 0.41$)

At discharge, a diagnosis of myocardial infarction was made by the treating physician in 57% of the cases, twice as much when compared with the working diagnosis at admission. However, according to the ACC/ESC criteria (based principally on the elevation of myocardial necrosis markers), 75% of the patients should have been classified as having suffered an acute myocardial infarction, a relative increase of 32% with respect to the clinical judgment.

Table 4 Risk stratification and invasive procedures

	All ($n = 1888$)	Hospitals without CathLab ($n = 915$)	Hospitals with CathLab ($n = 973$)	P^a
Early non-invasive evaluation				
Echo examination within 24 h (%)	1278 (67.7)	671 (73.3)	607 (62.4)	<0.0001
ST-segment monitoring (%)	853 (45.2)	428 (46.8)	425 (43.7)	0.22
Functional risk stratification				
Stress echo (%)	60 (3.2)	29 (3.2)	31 (3.2)	0.97
Exercise test (%)	199 (10.5)	125 (13.7)	74 (7.6)	<0.0001
Stress test + scintigraphy (%)	14 (0.7)	7 (0.8)	7 (0.7)	0.91
Holter monitoring (%)	190 (10.1)	128 (14.0)	62 (6.4)	<0.0001
Coronary angiograms (at 30-day)[b] (%)	1253 (67.0)	484 (53.5)	769 (79.7)	<0.0001
Initial admission (%)	1094 (57.9)	354 (38.7)	740 (76.1)	<0.0001
After discharge (%)[c]	160 (9.0)	138 (16.0)	22 (2.4)	<0.0001
PCI (at 30-day)[d] (%)	622 (33.3)	224 (24.8)	398 (41.3)	<0.0001
Initial admission (%)	540 (28.6)	157 (17.2)	383 (39.4)	<0.0001
After discharge (%)	97 (5.4)	81 (9.4)	16 (1.7)	<0.0001
CABG (at 30-day)[e] (%)	209 (11.2)	85 (9.4)	124 (12.9)	0.0170
Initial admission (%)	116 (6.1)	34 (3.7)	82 (8.4)	<0.0001
After discharge (%)	105 (5.9)	58 (6.7)	47 (5.1)	0.14
IABP initial admission (%)	6 (0.3)	3 (0.3)	3(0.3)	0.94

[a]Not adjusted for multiple comparisons.
[b]Known for 1869 patients (904 patients in hospital without CathLab, 965 in hospital with CathLab).
[c]Percentages after discharge are calculated on the 1784 patients discharged alive within 30 days (861 in hospital without CathLab, 923 in hospital with CathLab).
[d]Known for 1867 patients (903 patients in hospital without CathLab, 964 in hospital with CathLab).
[e]Known for 1864 patients (903 patients in hospital without CathLab, 961 in hospital with CathLab).

Overall, in-hospital mortality was 1.2%, with no deaths among patients younger than 55 years, up to 3.0% in those older than 75 years.

Thirty-day follow-up data were complete in 99% of the patients. One hundred and three patients had the composite endpoint (death, in-hospital myocardial infarction, and re-admission for ACS) at 30 days. As shown in *Table 8*, patients admitted to hospitals with an on-site CathLab experienced significantly fewer cardiac and cerebrovascular ischaemic events and tended towards lower mortality and heart failure. However, as shown in *Table 9*, admission to a hospital without an on-site CathLab did not result in an independent predictor of adverse outcome (death, in-hospital myocardial infarction, and re-admission for ACS) at 30 days: at multivariable analysis, this unfavourable composite endpoint was independently predicted only by increasing age and Killip class >1.

Pharmacological treatments

Pharmacological therapies used during hospitalization and at discharge are shown in *Figure 2*. At discharge, an anti-platelet treatment was prescribed to 88% of patients. Ticlopidine and clopidogrel use was influenced by PCI treatment. Among PCI-treated patients, ticlopidine was used in 25% of the cases and clopidogrel in 62% (35% with loading dose). In patients not treated by PCI, ticlopidine, and clopidogrel were, respectively, used in 14 and 24% (8.9% loading dose) of the cases. Low-molecular weight heparin was by far the most used antithrombin (59%) and was used slightly less frequently (52%) in patients also receiving a GpIIb–IIIa blocker. Any GpIIb–IIIa blocker was administered in 26% of the entire population (23% in hospitals without vs. 29% in hospital with CathLab, $P = \text{ns}$). Among PCI-treated patients, 49% received a GpIIb–IIIa blocker, up-stream in 63% of cases (19% of PCI patients transferred from hospitals without CathLab were already on GpIIb–IIIa blocker). Abciximab was used in 17% of cases (in 52% of cases, the drug was initiated in CathLab), tirofiban in 77% of the patients (started in 77% of cases in CCU), and eptifibatide in 7.4% of patients (started in 61% in CCU). Irrespective of the type of strategy, the use of GpIIb–IIIa blockers in diabetic patients did not differ from the general population. ACE-inhibitors and statins were initiated in most patients already during the hospital course.

Discussion

The BLITZ-2 study enrolled consecutive patients with NSTEACS admitted to a representative sample of the Italian cardiology units, with a wide range of access to diagnostic and interventional facilities. The survey took place in 2003, 1 year after the publication of the 2002 editions of the practice guidelines on NSTEACS by both the American and the European cardiological societies.[4,5] Therefore, it offers a unique opportunity to assess: (i) the impact of guideline recommendations on clinical practice; (ii) to which extent therapeutic strategies are based on risk stratification; (iii) the impact of resource availability on treatment strategy; and (iv) the relationship between

Table 5 Type of strategy according to risk profile

	All[b]	Conservative strategy ($n = 843$)	Invasive strategy ($n = 1039$)	P^a
Sex (%)				
Male	1278 (67.9)	525 (62.3)	753 (72.5)	<0.0001
Female	604 (32.1)	318 (37.7)	286 (27.5)	
Age (years) (%)				
<55	301 (15.9)	103 (12.2)	198 (19.1)	<0.0001
55–74	978 (52.1)	396 (47.0)	582 (56.0)	
>74	603 (32.0)	344 (40.8)	259 (24.9)	
Systolic blood pressure (mmHg) (%)				
<100	46 (2.4)	20 (2.4)	26 (2.52)	0.8560
≥100	1836 (97.6)	823 (97.6)	1013 (97.5)	
Heart rate (bpm) (%)				
≤100	1668 (88.6)	720 (85.4)	948 (91.2)	<0.0001
>100	214 (11.4)	123 (14.6)	91 (8.8)	
History of ischaemic heart disease (%)	856 (45.5)	422 (50.1)	434 (41.8)	0.0003
Killip Class (%)				
Class 1	1517 (80.6)	621 (73.7)	896 (86.2)	<0.0001
Class >1	365 (19.4)	222 (26.3)	143 (13.8)	
TIMI risk score (%)				
1–2	250 (13.3)	116 (13.8)	134 (12.9)	0.0109
3–4	948 (50.4)	393 (46.6)	555 (53.4)	
5–7	684 (36.3)	334 (39.6)	350 (33.7)	
ECG (%)				
Normal	275 (14.6)	119 (14.1)	156 (15.0)	0.0397
T wave negative	534 (28.3)	223 (26.5)	311 (29.9)	
ST-depression	930 (49.5)	446 (52.9)	484 (46.6)	
ST-elevation (transient)	143 (7.6)	55 (6.5)	88 (8.5)	
Positive biochemical necrosis marker[c] (%)	1387 (75.0)	611 (73.4)	776 (76.2)	0.18
Diabetes (%)	515 (27.3)	265 (31.4)	250 (24.1)	0.0004
ECG + marker (%)				
ST-depression + positive marker	703 (37.4)	333 (39.5)	370 (35.6)	0.08
Other combination of ECG/markers	1179 (62.6)	510 (60.5)	669 (64.4)	
ECG + marker + diabetes (%)				
ST-depression + positive marker + diabetes	219 (11.6)	120 (14.2)	99 (9.5)	0.0015
Other combinations	1663 (88.4)	723 (85.8)	940 (90.5)	

[a]Not adjusted for multiple comparisons.
[b]Strategy known for 1882 patients.
[c]Known for 1851 patients (832 patients in hospital without CathLab, 1019 in hospital with CathLab).

patient risk, treatment strategies, and outcome in an unselected patient population.

Patient risk profile

The BLITZ-2 study population resulted to be at relatively high-risk when compared with those enrolled in randomized trials,[2] with a higher prevalence of elderly patients (32% > 75 years), diabetics (27%), and patients with previous history of cardiac disease (47%), but similar to those of other surveys.[11] Patients admitted to hospitals without CathLab showed a worse risk profile in terms of age, diabetes, history of chronic angina, and heart failure on admission. In contrast, those admitted to hospitals with CathLab more frequently had had prior myocardial revisualizations, probably due to patients' self-referral and to a higher prevalence of revascularized citizens in the respective referral area.

Risk stratification and revascularization procedures

Until the end of the last decade, the functional risk stratification of patients with a cooled-off acute coronary syndrome was considered to be the standard therapeutic approach, as the alternative approach of routine coronary angiography and revascularization had showed no additional benefit.[12,13] On the basis of the results of more recent randomized clinical trials,[1–3] current guidelines[4,5] recommend an early invasive strategy in patients at intermediate and high-risk according to clinical, biochemical, and ECG stratification or according to composite risk scores, such as the TIMI risk score.[14] This recommendation is based on the

Table 6 Patients treated by invasive strategy according to risk profile and type of hospital

	All	OR (CI)[a]	Hospitals without CathLab	OR (CI)[a]	Hospitals With CathLab	OR (CI)[a]
Sex (%)						
Male	753/1278 (58.9)	1	231/595 (38.8)	1	522/683 (76.4)	1
Female	286/604 (47.4)	0.63 (0.51–0.77)	96/319 (30.1)	0.68 (0.50–0.92)	190/285 (66.7)	0.62 (0.45–0.84)
Age (years) (%)						
<55	198/301 (65.8)	1	60/131 (45.8)	1	138/170 (81.2)	1
55–74	582/978 (59.5)	0.77 (0.58–1.00)	174/452 (38.5)	0.74 (0.50–1.10)	408/526 (77.6)	0.80 (0.52–1.24)
>74	259/603 (43.0)	0.39 (0.29–0.52)	93/331 (28.1)	0.46 (0.30–0.70)	166/272 (61.0)	0.36 (0.23–0.57)
Systolic blood pressure (mmHg) (%)						
<100	26/46 (56.5)	1.06 (0.56–2.01)	13/26 (50.0)	1.83 (0.77–4.34)	13/20 (65.0)	0.66 (0.24–1.98)
≥100	1013/1836 (55.2)	1	314/888 (35.4)	1	699/948 (73.7)	1
Heart rate (bpm) (%)						
≤100	948/1668 (56.8)	1	289/790 (36.6)	1	659/878 (75.1)	1
>100	91/214 (42.5)	0.56 (0.42–0.76)	38/124 (30.7)	0.77 (0.50–1.17)	53/90 (58.9)	0.48 (0.30–0.77)
History of ischaemic heart disease (%)						
No	605/1026 (59.0)	1	181/489 (37.0)	1	424/537 (79.0)	1
yes	434/856 (50.7)	0.72 (0.59–0.86)	146/425 (34.4)	0.89 (0.67–1.18)	288/431 (66.8)	0.54 (0.40–0.72)
Killip Class (%)						
Class 1	896/1517 (59.1)	1	271/701 (38.7)	1	625/816 (76.6)	1
Class >1	143/365 (39.2)	0.45 (0.35–0.57)	56/213 (26.3)	0.57 (0.40–0.80)	87/152 (57.2)	0.41 (0.28–0.59)
TIMI risk score (%)						
1–2	134/250 (53.6)	1	44/126 (34.9)	1	90/124 (72.6)	1
3–4	555/948 (50.4)	1.22 (0.92–1.62)	175/452 (38.7)	1.18 (0.78–1.78)	380/496 (76.6)	1.24 (0.79–1.93)
5–7	350/684 (51.2)	0.91 (0.68–1.21)	108/336 (32.1)	0.88 (0.57–1.36)	242/348 (69.5)	0.86 (0.55–1.36)
ECG (%)						
Normal	156/275 (56.7)	1	51/138 (37.0)	1	105/137 (76.6)	1
T wave negative	311/534 (58.2)	1.06 (0.79–1.43)	97/244 (39.8)	1.13 (0.73–1.73)	214/290 (73.8)	0.86 (0.53–1.38)
ST-depression	484/930 (52.0)	0.83 (0.63–1.09)	156/471 (33.1)	0.85 (0.57–1.25)	328/459 (71.5)	0.76 (0.49–1.19)
ST-elevation (transient)	88/143 (61.5)	1.22 (0.81–1.84)	23/61 (37.7)	1.03 (0.55–1.92)	65/82 (79.3)	1.17 (0.60–2.27)
Biochemical necrosis marker[b] (%)						
Negative	243/464 (52.4)	1	90/240 (37.5)	1	153/224 (68.3)	1
Positive	776/1387 (56.0)	1.16 (0.94–1.43)	234/666 (35.1)	0.90 (0.66–1.24)	542/721 (75.2)	1.41 (1.00–2.00)
Diabetes (%)						
No	789/1367 (57.7)	1	246/646 (38.1)	1	543/721 (75.3)	1
Yes	250/515 (48.5)	0.69 (0.56–0.85)	81/268 (30.2)	0.70 (0.52–0.97)	169/247 (68.4)	0.71 (0.51–0.99)
ECG + marker (%)						
Other combination of ECG/markers	669/1179 (56.7)	1	215/568 (37.9)	1	454/611 (74.3)	1
ST-depression + positive marker	370/703 (52.6)	0.85 (0.70–1.03)	112/346 (32.4)	0.79 (0.59–1.05)	258/357 (72.3)	0.90 (0.67–1.23)
ECG + marker + diabetes (%)						
Other combinations	940/1663 (56.5)	1	294/794 (37.0)	1	646/869 (74.3)	1
ST-depression + positive marker + diabetes	99/219 (45.2)	0.63 (0.47–0.85)	33/120 (27.5)	0.65 (0.41–1.00)	66/99 (66.7)	0.69 (0.44–1.11)

[a]Unadjusted.
[b]Known for 1851 patients (906 patients in hospital without CathLab, 945 in hospital with CathLab).

Table 7 Predictors of invasive strategy

Variables	Reference category	Univariate *P*	Multivariate				
			χ^2	Odds ratio	95%CI		*P*
CathLab on-site	No vs. yes	<0.0001	230.383	4.810	3.921	5.882	<0.0001
Age	Continuous	<0.0001	20.528	0.979	0.970	0.988	<0.0001
Heart rate on admission	Continuous	<0.0001	15.981	0.990	0.985	0.995	<0.0001
Killip Class	>1 vs. 1	<0.0001	5.920	0.714	0.541	0.942	0.0172
Biochemical necrosis marker	Positive vs. negative	0.180	4.234	1.191	0.940	1.510	0.1482
Sex	Female vs male	<0.0001	3.343	0.806	0.644	1.010	0.0604
History of ischaemic heart disease	Yes vs. no	0.0003	2.627	0.831	0.671	1.029	0.0894
Systolic blood pressure on admission	Continuous	0.630	1.371	1.002	0.998	1.006	0.2478
Diabetes	Yes vs. no	0.0004	0.978	0.887	0.704	1.118	0.3096
ST-segment depression	Yes vs. no	0.0064	0.004	1.009	0.819	1.243	0.9363

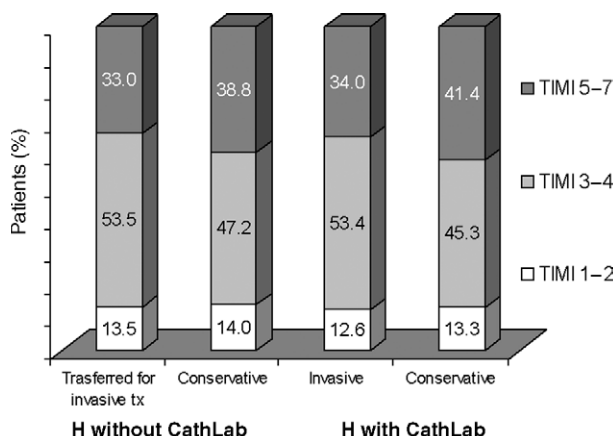

Figure 1 TIMI risk score according to strategy and type of hospital. TIMI, TIMI risk score for NSTE acute coronary syndromes; H, hospital; tx, strategy.

observation that the benefit from revascularization procedures is confined to moderate and high-risk patients.[2,15,16] According to the present survey, in everyday clinical practice patient selection for coronary angiography does not seem to depend on the clinical, electrocardiographic, and biochemical predictors of worse outcome. Overall, about half of the patients with ST-segment depression and elevated myonecrosis markers and a half of those with diabetes did not undergo coronary angiography during the index hospital admission. Instead, a strikingly different approach was observed according to the on-site access to a catheterization laboratory, as 73% of the patients admitted to hospitals with interventional CathLab were treated invasively when compared with 36% of those admitted to hospitals without invasive capability. In contrast, by stratifying the patients according to the TIMI-NSTEACS score, we observed that in both hospital categories, the indication for early coronary angiography was placed irrespective of risk profile. Similar data have been reported earlier, starting from the OASIS registry[17] down to the recent CRUSADE registry.[6] One possible explanation for this invariable finding of registries might be the inability of data collection to depict non-cardiac comorbidities that may impact on clinical decision. However, looking at the data from a health-care perspective, the BLITZ-2 registry shows sub-optimal use of existing resources as both over-treatment of low-risk patients and under-treatment of those at high-risk. As far as the low-risk patients are concerned, a recent analysis of the TIMI-3B trial[18] showed that an invasive strategy in these patients was not cost-effective, because, in that database, it would have implied an additional cost of $2 695 700 without reducing the risk of death or AMI, though with the advantage of 34 fewer rehospitalizations. This expenditure of $79 285 per hospitalization prevented far exceeded the monetary cost of rehospitalization ($14 000). However, the observation that high-risk patients are not receiving highly effective therapies is much more disappointing and represents the challenge for better use of existing resources both in hospitals with and without interventional facilities. In the present registry, 39% of the patients admitted to hospitals without interventional facilities were transferred for coronary angiography and revascularization, however, with an 'inverse' stratification favouring the transfer of low- and moderate-risk patients. However, in these hospitals, only ~15% of patients underwent functional stratification. This attitude is the most frustrating finding of the present registry, as an invasive approach in high-risk patients has been shown to reduce the risk of death by 45%, myocardial infarction and rehospitalization for ACS at 30 days.[2] A similarly disappointing finding is the strictly conservative approach used in elderly patients in our registry, as well as in CRUSADE,[6] despite the fact that both randomized trials[19] and registries[20] indicate that an aggressive approach may be particularly effective in the elderly and age results an independent predictor of adverse outcome. The reasons why high-risk and elderly patients are denied effective treatments, whereas lower risk patients are managed more aggressively, remain to be clarified. One reason for this attitude may be clinical judgement that prioritize patients with longer life-expectancy (younger patients) rather than high-risk elderly patients who might benefit in the short-term, but not in the long-term. It might also be that invasive cardiologists are more reluctant to accept patients, in whom 'a priori' coronary angiography may be less likely to show lesions not suitable for PCI, owing to diffuse disease and less identifiable culprit lesion. Contrary to this thinking, our data show that the ratio between the numbers of PCIs and coronary angiograms does not differ according to age (0.49 in patients $\leq$74 years and 0.52 in patients >74 years, $P = 0.3094$). Another possibility is that an aggressive

Table 8 Hospital course and 30-day follow-up

	All ($n = 1888$)	Hospitals without CathLab	Hospitals with CathLab	OR (CI)	*P*
Ischaemic complications (%)	134 (7.1)	82 (9.0)	52 (5.3)	1.74 (1.22–2.50)	0.003
Recurrent angina-ischaemia (%)	108 (5.7)	68 (7.4)	40 (4.1)		0.002
NSTE-MI (%)	12 (0.6)	7 (0.8)	5 (0.5)		0.50
STE-MI (%)	7 (0.4)	4 (0.4)	3 (0.3)		0.64
Periprocedural MI (Q-MI)	8 (0.4)	2 (0.2)	6 (0.6)		0.18
Non-ischaemic complications (%)	147 (7.8)	86 (9.4)	61 (6.3)	1.55 (1.10–2.18)	0.012
Heart failure (%)	58 (3.1)	33 (3.6)	25 (2.6)		0.19
Cardiogenic shock (%)	27 (1.4)	17 (1.9)	10 (1.0)		0.13
Stroke (%)	8 (0.4)	6 (0.7)	2 (0.2)		0.13
Minor bleeding (%)	28 (1.5)	16 (1.8)	12 (1.2)		0.36
Major bleeding (%)	24 (1.3)	12 (1.3)	12 (1.2)		0.88
Ventricular arrhythmias (%)	31 (1.6)	19 (2.1)	12 (1.2)		0.15
Patients discharged alive[a] (%)	1800 (95.3)	870 (95.1)	930 (95.6)	0.89 (0.58–1.37)	0.69
Discharged home (%)	1500 (83.3)	703 (80.8)	797 (85.7)		<0.007
Transferred for rehabilitation (%)	85 (4.7)	24 (2.8)	61 (6.6)		<0.0001
Transferred to other H (%)	215 (11.9)	143 (16.4)	72 (7.7)		<0.0001
Death (%)	22 (1.2)	12 (1.3)	10 (1.0)	1.28 (0.56–2.91)	0.72
Patients still admitted at 30 days (%)	59 (3.1)	31 (3.4)	28 (2.9)	1.18 (0.71–1.98)	0.61
Events at 30 days[b]					
Death (%)	45 (2.4)	26 (2.9)	19 (2.0)	1.47 (0.82–2.66)	0.2
Cardiac ischaemic events[c] (%)	172 (9.2)	104 (11.5)	68 (7.1)	1.71 (1.24–2.35)	0.0009
Heart failure (%)	91 (4.9)	52 (5.8)	39 (4.1)	1.44 (0.95–2.20)	0.09
Stroke (%)	17 (0.9)	14 (1.6)	3 (0.3)	5.03 (1.54–16.4)	0.005

[a]For seven patient discharge data are missing; (1800 discharged alive, 870 patients from hospital without CathLab, 930 from hospital with CathLab).
[b]Data available on 1865 patients (903 patients in hospital without CathLab, 962 patients in hospital with CathLab).
[c]In hospital ischaemic complications plus re-admissions for acute coronary syndrome.

Table 9 Predictors of death, in-hospital myocardial infarction, and re-admission for acute coronary syndromes at 30 days (evaluated on 1865/1888 patients, 103 events)

Variables	Reference category	Univariate *P*	Multivariable				
			χ^2	Odds ratio	95%CI		*P*
Age	Continuous	<0.0001	15.571	1.043	1.021	1.065	0.0001
Killip Class	>1 vs. 1	<0.0001	4.194	1.633	1.020	2.614	0.0412
Systolic blood pressure on admission	Continuous	0.472	2.339	0.994	0.987	1.002	0.1294
Diabetes	Yes vs. no	0.045	0.899	1.233	0.800	1.900	0.3431
ST-segment depression	Yes vs. no	0.039	0.712	1.198	0.785	1.827	0.4031
Biochemical necrosis marker	Positive vs. negative	0.280	0.297	1.184	0.710	1.975	0.5179
CathLab on-site	No vs. yes	0.214	0.219	1.104	0.734	1.660	0.6361
Heart rate on admission	Continuous	0.062	0.046	1.001	0.992	1.010	0.8450
Sex	Female vs. male	0.198	0.034	0.959	0.619	1.484	0.8494
History of ischaemic heart disease	Yes vs. no	0.151	0.001	1.011	0.664	1.541	0.9578

pharmaco-interventional approach in patients with prior cardiac events or revascularizations and in those with severe co-pathologies requires very experienced personnel and a multidisciplinary approach that may not be available at any hospital. Developing the culture of acute coronary care in high-risk patients is the challenge for the years to come.

Outcome

Among the possible reasons for being rather conservative may be the satisfaction with a mortality rate of as low as 2.4% at 30 days observed in the present registry. Other unfavourable outcomes, such as re-admissions for ACS and heart failure were also low in the population as a whole. Recent Italian registries, such as ROSAI-2, showed higher 30-day mortality and infarction rates despite comparable entry criteria.[20] It is unlikely that selection bias might have played a role, as the overall risk profile according to the TIMI risk score was higher in the BLITZ-2 population. In the GUSTO IV study,[21] which had a mortality rate of 3.9% at 30 days, the percentage of patients with both ST-depression and troponin positivity was 31% when compared

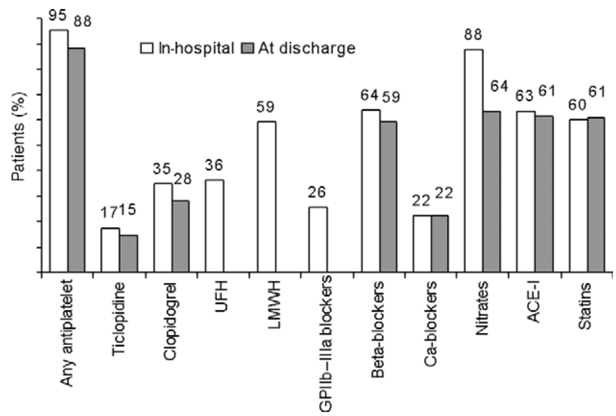

Figure 2 Pharmacological treatment. UFH, unfractionated heparin; LMWH, low-molecular weight heparin; ACE-I, ACE-inhibitors; Ca-blockers, calcium channel blockers.

with 38% in BLITZ-2; also the percentage of diabetic patients was higher in our survey (27.3 vs. 21%) when compared with GUSTO IV. Another possibility may be that invasive strategies, clopidogrel, and glycoprotein blockers were used more frequently in the present survey when compared with other studies. Contemporary to our survey, the SINERGY trial,[22] where age > 60 years was one of the qualifying criteria, recorded a 30-day mortality of 3.2%, very close to the 2.8% mortality observed in BLITZ-2 patients $>$55-year-old. A slightly better outcome (with mortality rate as low as 2.2%) was observed in the invasive arm of the TACTICS-TIMI 18 study (with 97% of the patients treated aggressively), which had similar entry criteria as BLITZ-2 (however, with only 15% of the patients with TIMI risk score of 5–7 when compared with 36% in BLITZ-2). Among the non-fatal outcomes, myocardial (re)infarctions occurring after hospital admission, and particularly those occurring after PCI, are clearly underestimated in clinical practice. As a matter of fact, when these events are specifically looked for, as in the PURSUIT[23] or in the GUSTO IV[21] trials, or in the recent CK-MB and PCI study,[24] they have been shown to occur in $\sim$10% of the cases following hospital admission and 15% following PCI, whereas ours and other registries had spontaneous reports of $\sim$1–2%. The failure to recognize the occurrence and prognostic importance[24,25] of these events, which may be prevented by timely pharmacological and interventional approach, may also explain the relative conservative approach observed in clinical practice.

Patients admitted to hospitals with an on-site CathLab experienced fewer cardiac events at 30 days when compared with those admitted to hospitals without CathLab; this difference included lower mortality, fewer cardiac ischaemic recurrences, as well as less heart failure and stroke. However, patients admitted to no-CathLab hospitals had a significantly higher prevalence of the only two factors resulting independent predictors of unfavourable outcome at multivariable analysis, namely, older age and Killip class $>$1; these patients also had a much higher incidence of atrial fibrillation on admission, which might explain the significantly higher stroke rate at 30 days. This unbalance in baseline patient characteristics, the low power of the study to investigate factors associated with different outcomes (with most of the well validated predictors resulting significant at univariate but not multivariable analysis) and the fact that the more aggressive therapy was not tailored to treat higher risk patients do not allow the conclusion that the presence of an on-site CathLab, and the subsequent more liberal use of coronary angiography and revascularization, provides better outcome. The different case-mix (in terms of co-morbidities and severity at admission) among specialty cardiac hospitals and general hospital also accounted for the different mortality rate in a large retrospective cohort study of Medicare patients.[26]

The importance of a tailored treatment according to patients' selection was also shown by a recently reported randomized clinical trial, the ICTUS Study,[27] compared with a selective invasive approach, a systematic invasive approach resulted in similar rates of death, new or recurrent MI, and rehospitalization for ACS when applied to patients selected only on the basis of a positive troponin. A recently reported analysis of the GRACE registry[11] on 28 000 ACS patients showed that admission to hospitals with CathLab was not associated with better short- and medium-term prognoses (6 months), despite the 10-fold difference in reperfusion rate and a 30-day mortality of 7.3% (very high-risk patients). The rate of percutaneous interventions in patients admitted to hospitals without invasive capabilities was strikingly low (4.6% in NSTEMI), suggesting the absence of a hub-and-spoke policy. However, the comparison among different surveys may be flawed by some methodological pitfalls, the most important of which is how the diagnosis of infarction is made. In the BLITZ survey[8] (enrolling in 2001) patients, final diagnosis of myocardial infarction was made by treating physician according to a provided definition including both the classical WHO[27] and the new ESC/ACC[9] ones (however, troponin I or T was used as unique biomarker only in 3% of cases). Thirty-day mortality for NSTEMI was 7.1%, very similar to 7.3% observed in GRACE (conducted since 1999, before publication of ESC/ACC definition), which used identical inclusion methodology. Differently, in BLITZ-2, the final diagnosis of myocardial infarction was adjudicated according to the level of biomarker reported, in 92% of cases troponin I or T. The 30-day mortality of the present population is comparable to the mortality of patients classified as unstable angina in GRACE (3.5% at 30 days).

Study limitations

Although the participating centres were asked to enrol all consecutive patients with a final diagnosis of acute coronary syndrome without ST-segment elevation, we were not able to verify this task, because of the lack of administrative auditing. Outcome results reflect those of patients admitted to coronary care units and may not apply to all of the patients admitted to cardiology departments and even less to patients with NSTEACS admitted to non-cardiological units. In addition, restriction of the registry to patients who are admitted may have resulted in the exclusion of patients who died early on arrival in the Emergency Department or were not able to sign the patients consent. Finally, some patients could be excluded from an invasive strategy because of their refusal.

However, we think that these limitations could not affect the main results of the survey concerning the organization-related factors and therapeutic management of patients with NSTEACS on a population of high-risk patients.

Conclusion

Despite clear-cut indications from recognized international guidelines, contemporary management of patients with NSTEACS in Italy reflects more closely what has been seen in worldwide registries rather than what has been proven effective in randomized clinical trials and is primarily driven by resource availability. Optimization of existing resources should include more aggressive treatment of high-risk patients both in hospitals with and in those without interventional facilities. On the basis of the results of the BLITZ-2 study, the Italian Hospital Cardiology Association (ANMCO and the national Health Authorities (Istituto Superiore di Sanità) decided to conduct an outcome research, using a permanent registry, on patients admitted to different types of hospital (both in cardiological and in internal medicine wards). This is a first step able to steer health policy to organizational and clinical improvements driven by the regulatory authorities.

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Conflict of interest: none declared.

Appendix

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