

Compliance of pharmacological treatment for non-ST-elevation acute coronary syndromes with contemporary guidelines: influence on outcomes

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Background: Although the proven efficacy of evidence-based therapy in patients with cardiovascular diseases, the recommendations are not always instituted. We aimed to analyse the compliance of non-ST-elevation acute coronary syndrome (NSTEMI-ACS) patients with treatment guidelines and to assess the impact of these measures in hospital death during the index hospitalization.

Population and methods: All consecutive patients (pts) included in the *Portuguese Registry on Acute Coronary Syndromes* (ProACS) between January 1, 2002 and August 31, 2011 were analysed. Compliance with Guidelines for the management of NSTEMI-ACS was evaluated with a 6-point therapeutic score (ThSc), comprising the treatment with: aspirin, clopidogrel, heparin, beta-blocker, angiotensin-converting enzyme inhibitor and statin. One point was assigned for each drug prescribed and zero if not given. The total therapeutic compliance was defined as ThSc =6 points.

Results: The final analysis comprised 14,276 pts (67.1% male; mean age 67.6±12.3 years), most of them admitted with non-ST elevation myocardial infarction (77.4%). The mean value of ThSc was 4.9±1.1 and total compliance occurred in 36.7% pts. Centres with percutaneous coronary intervention (PCI) capacity had a statistically significant higher ThSc (5.0±1.0 vs. 4.8±1.1, P<0.001) and were associated with higher total compliance [OR 1.53, 95% confidence intervals (CI), 1.42-1.65, P<0.001]. In-hospital mortality was 2.4% (354 deaths). Compared to pts who died, the survivors had a higher ThSc (4.9±1.1 vs. 4.2±1.3, P<0.001) and this score was independently associated with lower risk of in-hospital mortality (OR 0.70, 95% CI, 0.64-0.77, P<0.001). Receiver operating characteristics curve analysis showed a good accuracy of ThSc for the occurrence of in-hospital mortality with the area under the curve (AUC) 0.82 (95% CI, 0.80-0.84, P<0.001), sensitivity 71.6% and specificity 78.0%. Age, peripheral artery disease, Killip-Kimball class >I, electrocardiogram (ECG) with ST-segment depression and positive troponin were other independent predictors of in-hospital mortality.

Conclusions: In the present study, patients with NSTEMI-ACS who received medications recommended by guidelines had better in-hospital outcomes. These findings highlight the need to clarify the clinical recommendations and to develop approaches for quality improvement in this subset of patients.

Keywords: Non-ST-elevation acute coronary syndrome (NSTEMI-ACS); compliance; guidelines



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Introduction

Non-ST-elevation acute coronary syndromes (NSTEMI-ACS) are associated with an increase risk of death and several other cardiovascular complications (1). However, over the last years, advances in cardiovascular care have resulted in a decline in mortality and morbidity associated with NSTEMI-ACS (2-4). Strong evidence shows that the best therapeutic strategies for these patients are not always followed, suggesting that outcomes of NSTEMI-ACS patients are not as good as they could be with better translation of the best scientific knowledge into clinical practice (5). This reality has been well demonstrated in the CRUSADE initiative (6) and in the Euro Heart Survey ACS (7). Thus, NSTEMI-ACS remains an important cause of premature mortality and morbidity with a considerable economic impact due to both direct and indirect costs.

The successful implementation of clinical guidelines, incorporating new treatments into practice, has been challenging and the adherence to the evidence-based treatment and its implications after ACS are poorly defined (8-11).

The aim of this study is to assess the compliance of NSTEMI-ACS patients with management Guidelines and to evaluate its impact on hospital outcomes.

Methods

Study design and population

All consecutive patients included in the *Portuguese Registry on Acute Coronary Syndromes* (ProACS) between January 1, 2002 and August 31, 2011 were eligible. This is a continuous, prospective and observational registry, with 46 participating centres that are cardiology departments of hospitals in the main land territory, and the Madeira and Azores islands (12,13). For the purpose of the present study, only patients with NSTEMI-ACS were included. A diagnosis of non-ST-elevation myocardial infarction (NSTEMI) was established according to the universal definition criteria for type 1 myocardial infarction (14). Those patients who died during the first 24 hours of hospitalization were excluded because of their intrinsic low likelihood of receiving certain evidence-based therapies, such as beta-blockers and angiotensin converting enzyme (ACE) inhibitors.

Data collected

All data were registered in a dedicated computer database, including demographic, clinical, patient management-related

characteristics, as well as clinical outcomes. Compliance with Guidelines for the management of NSTEMI-ACS (15) was classified according to the value of a therapeutic score (ThSc) based on the recommended pharmacological therapies received during hospitalization. This guideline-adherence score comprised the following treatments: aspirin, clopidogrel, heparin, beta-blocker, ACE-inhibitor and statin. For each of these drugs one point was assigned if taken and zero if not. Total therapeutic compliance was defined as a ThSc of six points (i.e., highest possible score). All decisions regarding the patient management strategy, including referral for coronary angiography and performance of myocardial revascularization, via percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), were left to the discretion of the attending physician and the site-specific protocols. All-cause death during the index hospitalization was used to assess the prognostic value of compliance with guideline-based treatment of NSTEMI-ACS.

Statistical analysis

Means and standard deviations (mean \pm SD) were used to describe continuous variables with normal distribution, and percentages for categorical variables. Normality was tested with the Kolmogorov-Smirnov test. Differences between baseline characteristics and outcomes were evaluated with the chi-square test (or Fisher's exact test, when appropriate) for categorical variables and the *t*-test for continuous variables. Adjusted risk estimates were obtained from a Cox logistic regression model (goodness of fit by Hosmer and Lemeshow test), which included all demographic (age; gender), clinical (atherothrombotic risk factors; prior history of myocardial infarction, PCI or CABG; prior stroke or transient ischemic attack; clinical peripheral arterial disease; baseline Killip-Kimball class), electrocardiographic (ST-segment depression on presentation) and biochemical marker (NSTEMI diagnosis) variables with a potential impact on the study endpoint. In the Cox model, the model assumptions (i.e., proportional hazards, linearity of continuous covariates, and lack of interactions) were found to be valid. Receiver operator characteristic (ROC) curve analysis (c-statistic) was used to identify the predictive accuracy of the ThSc for in-hospital death with determination of the area under the curve (AUC), sensitivity and specificity. Two-tailed tests of significance are reported. For all comparisons, a *P* value <0.05 was considered statistically significant. When appropriate, 95% confidence intervals (CI) were calculated.

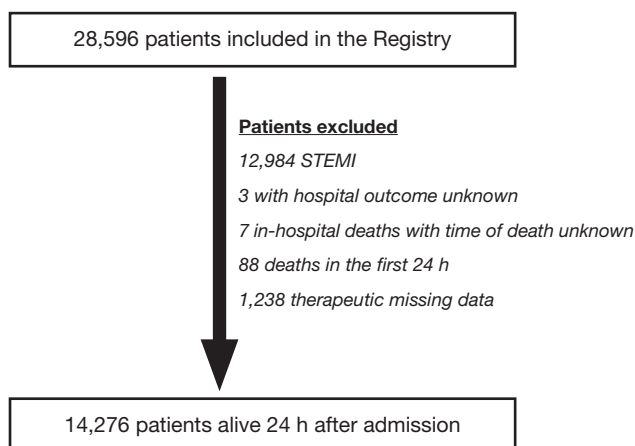


Figure 1 Flowchart showing the number of patients excluded and included in the final analysis of the study.

Statistical analysis was performed with SPSS version 19.0 (SPSS Inc., Chicago, IL, USA).

Results

Of the 28,596 patients included in the Registry during the study period, 14,083 were excluded. The final analysis comprised a total of 14,276 patients (*Figure 1*).

Baseline characteristics of the study cohort are shown in the *Table 1*. The mean age is 67.6 ± 12.3 years, most patients are male (67.1%) and the presence of atherothrombotic risk factors and clinically overt cardiovascular disease is common: over two thirds have a history of hypertension and a quarter of myocardial infarction; 16.4% have undergone myocardial revascularization via PCI or CABG. Prior use of aspirin, beta-blocker, ACE-inhibitor, and statin is relatively low.

Regarding the clinical presentation at hospital admission, almost half of the patients (45.5%) were symptomatic with typical chest pain at rest on admission, 77.5% referred at least one episode of angina at rest lasting more than 20 minutes and 34.4% referred recurrent episodes of angina. Physical signs of heart failure (Killip-Kimball class >1) were present in 19.2% patients at admission. The most common type of NSTEMI-ACS was NSTEMI (77.4%): ST-segment depression was detected on the baseline electrocardiogram (ECG) in 36.6% patients.

In-hospital management is described in *Table 2*. A heparin was prescribed in 95.8% patients, aspirin in 96.9%, a thienopyridine in 66.6%, a beta-blocker in 72.7%, an ACE-inhibitor in 73.6% and a statin in 86.8%. The mean ThSc was 4.9 ± 1.1 and 36.7%

Table 1 Baseline characteristics of the population studied

Variables	Percentage (%)
Demographic	
Male gender	67.1
Age (years) [mean \pm SD]	67.6 ± 12.3
Atherothrombotic risk factors	
Diabetes	30.1
Hypertension	67.9
Hypercholesterolemia	48.1
Current smoking	18.3
Prior cardiovascular disease	
Stroke/TIA	7.6
Peripheral artery disease	3.9
MI	24.9
PCI	10.2
CABG	6.2
Prior pharmacological therapy	
Aspirin	31.6
Beta-blocker	20.9
ACE-inhibitor	29.3
Statin	27.8

ACE, angiotensin converting-enzyme; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; MI, myocardial infarction; TIA, transient ischemic attack.

patients had total compliance (i.e., ThSc =6).

Figure 2 shows the distribution of all patients according to the ThSc value. *Figure 3* presents the mean value of ThSc per study site. The mean ThSc was significantly higher in sites with PCI capacity (5.0 ± 1.0 vs. 4.8 ± 1.1 , $P < 0.001$) as was the rate of total compliance (41.1% vs. 30.8%, $P < 0.001$). Coronary angiography was performed in 66.8% patients and 35.8% underwent myocardial revascularization (PCI 33.9% and CABG 1.9%) during the index hospitalization.

The incidence of in-hospital death was 2.4% (354 deaths). Patients who survived to hospital discharge differed significantly from those who died with respect to clinical characteristics (*Table 3*). Mean ThSc was higher among patients who survived (4.9 ± 1.1 vs. 4.2 ± 1.3 , $P < 0.001$). In-hospital mortality was inversely distributed according to the value of ThSc (*Figure 4*) and was similar in sites with and without PCI capacity (2.3% vs. 2.7%, $P = 0.107$).

Table 4 shows the results of the multivariable analysis for identifying the independent predictors of in-hospital

mortality. ThSc was independently associated with higher in-hospital survival (OR 0.70, 95% CI, 0.64-0.77; P<0.001). Age, peripheral artery disease, Killip-Kimball class >I, ECG with ST-segment depression and positive troponin were

independent predictors of in-hospital death.

In a ROC curve analysis, ThSc showed a good predictive accuracy for the occurrence of in-hospital death: AUC =0.82 (95% CI, 0.80-0.84; P<0.001), sensitivity 71.6%, and specificity 78.0%. Table 5 presents the independent predictors of total compliance with the score of recommended therapies (ThSc =6). Among these are the majority of the traditional cardiovascular risk factors, previous myocardial revascularization, positive troponin, and admission to a site with PCI capacity. Older patients, women, smokers and patients with heart failure at admission (Killip-Kimball class >I) were less likely to be associated with total compliance with the score.

Table 2 In-hospital management (%)

Pharmacological therapy	
Aspirin	96.9
Clopidogrel/ticlopidine	66.6
Any heparin	95.8
UFH	12.5
LMWH	92.0
Glycoprotein IIb/IIIa inhibitor	27.6
Nitrate	87.0
Beta-blocker	72.7
CCB	19.0
ACE inhibitor	73.6
Statin	86.9
Coronary angiography	
PCI	33.9
CABG	1.9
Myocardial revascularization	
PCI	33.9
CABG	1.9

ACE, angiotensin converting-enzyme; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; CCB, calcium channel blocker; LMWH, low molecular weight heparin; UFH, unfractionated heparin.

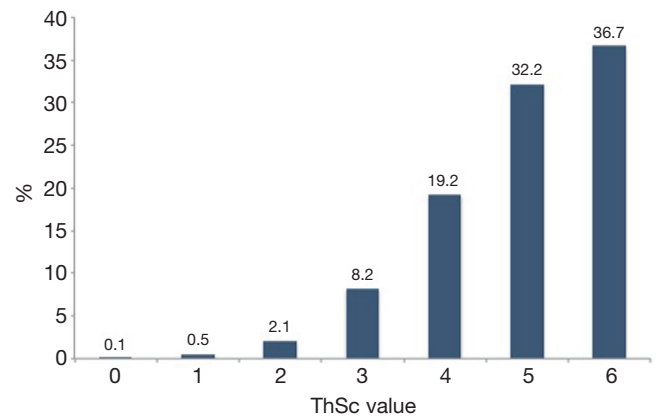


Figure 2 Distribution of the population studied according to the ThSc value.

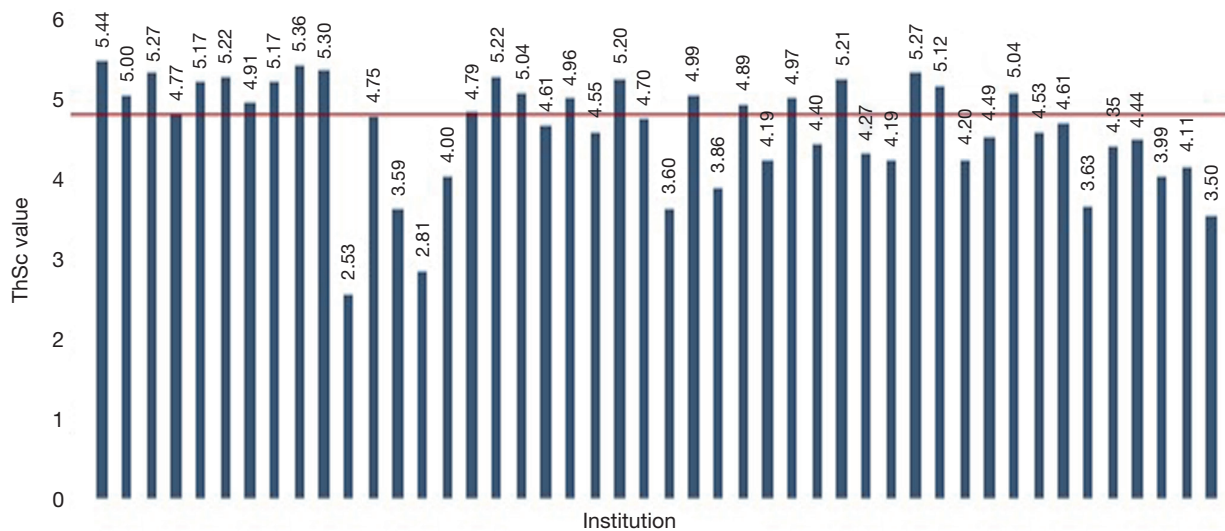


Figure 3 Average compliance score per study site.

Table 3 Differences between patients who died during hospitalization and those who survived to discharge (univariate analysis)

Characteristics (%)	Dead	Alive	P value
Age (year)	77.2±9.2	67.4±12.3	<0.001
Male gender	58.2	67.3	<0.001
Diabetes mellitus	35.2	29.9	0.033
Hypercholesterolemia	33.8	48.5	<0.001
Smoking	7.2	18.6	<0.001
Prior stroke/TIA	13.8	7.5	<0.001
Prior PAD	9.2	3.8	<0.001
Prior MI	30.7	24.7	0.011
Prior PCI	4.9	10.4	0.001
Prior ACE inhibitor	35.8	29.1	0.007
Angina lasting >20 min	71.9	77.7	0.011
Killip-Kimball class >I	58.4	18.2	<0.001
ST-segment depression	59.1	36.0	<0.001
Positive troponin	91.1	77.1	<0.001
TIMI score >3	52.5	30.9	<0.001
Aspirin	92.0	97.0	<0.001
Thienopyridine	49.6	67.0	<0.001
Beta-blocker	44.4	73.4	<0.001
CCB	12.0	19.2	0.001
ACE inhibitor	68.2	73.7	0.021
Statin	75.1	87.2	<0.001
ThSc	4.2±1.3	4.9±1.1	<0.001
Coronary angiography	30.5	66.6	<0.001
PCI	13.2	34.4	<0.001

ACE, angiotensin converting-enzyme; CCB, calcium channel blocker; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; TIA, transient ischemic attack, ThSc, therapeutic score.

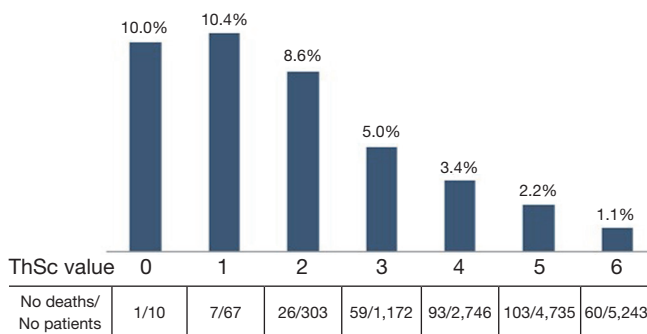


Figure 4 Distribution of the rate of in-hospital mortality according to the ThSc value.

Table 4 Independent predictors of in-hospital death

Characteristics	OR	95% CI	P value
ThSc (per unit)	0.70	0.64-0.77	<0.001
Age (per year)	1.06	1.05-1.07	<0.001
Peripheral artery disease	2.59	1.73-3.88	<0.001
Killip-Kimball class >I	3.13	2.45-4.01	<0.001
ECG ST-segment depression	1.66	1.30-2.10	<0.001
Positive troponin	2.30	1.48-3.56	<0.001

ECG, electrocardiogram.

Table 5 Independent predictors of total compliance with the score (ThSc =6)

Characteristics	OR	95% CI	P value
Age (per year increase)	0.98	0.98-0.99	<0.001
Female gender	0.88	0.81-0.96	0.003
Diabetes	1.22	1.12-1.32	<0.001
Hypertension	1.62	1.49-1.77	<0.001
Hypercholesterolemia	1.42	1.32-1.63	<0.001
Smoking	0.86	0.77-0.95	0.005
Prior PCI	1.28	1.14-1.45	<0.001
Prior CABG	1.17	1.00-1.37	0.044
Killip-Kimball class >I	0.69	0.62-0.76	<0.001
Positive troponin	1.83	1.66-2.02	<0.001
PCI capacity	1.53	1.42-1.65	0.001

CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention, ThSc, therapeutic score.

Discussion

The present study shows that compliance with evidence-based medical therapy in patients admitted with NSTEMI-ACS is strongly associated with lower hospital mortality. For each evidence-based drug class included in the management of the patient, hospital mortality was 30% lower than in patients who did not receive the drug. Patients receiving all recommended therapies had the highest rate of survival to discharge. Yet, this latter group comprised only 36.7% of patients, thus showing that recommended therapy is not delivered to the majority of NSTEMI-ACS patients.

Over the past years, the use of evidence-based therapies with proven efficacy in reducing morbidity and mortality in patients with cardiovascular diseases has increased significantly (16-18), yet large room for improvement persists. In the setting of ACS, adherence to evidence-based

therapies is lower in patients with NSTEMI compared to those with ST-elevation myocardial infarction (19). Guidelines on NSTEMI-ACS have undergone several revisions since 2002, when this registry began including patients. Nevertheless, the six pharmacological interventions used in the present score were already recommended in the Guidelines of European Society of Cardiology (20).

Better quality of care is expected to favorably impact on the economic and social burdens of ischemic heart disease (21). Data regarding the association between clinical performance and outcomes are limited. Peterson *et al.* (22) showed in ACS patients that every 10% increase in composite adherence at a hospital was independently associated with an analogous 10% decrease in the patients' likelihood of in-hospital mortality. As in the study by Roe *et al.* (23), in our experience, patients with highest risk are less likely to receive guideline-recommended therapies and interventions. Such patients include those with heart failure manifestations at admission, older patients and smokers. Patients with a higher baseline risk of adverse outcomes are expected to have a greater absolute benefit from aggressive therapies. Women and elderly patients were also less likely to receive evidence-based therapies, as demonstrated in the CRUSADE Quality Improvement Initiative (24). Several factors may explain this finding in these subgroups of patients, namely the higher frequency of comorbidities, contra-indications for drug therapy and atypical symptoms. In our study, centres with PCI capacity showed better adherence to guideline recommendations, a finding also previously reported (24).

Our data also suggest that the use of guideline-based process measures may be an important means of assessing quality of care, and this hypothesis deserves further study. Nevertheless, there is considerable debate regarding the ideal methodologies for assessing clinical performance (25). Quality of care may be improved by the use of tools that facilitate the implementation of guideline recommendations at different levels, namely the institution, the care provider, and the patient (26). Quality of care can be evaluated in three domains: structure (aspects that exist independently of the patient), process (actions performed in delivering care), and outcomes (events that occur as a result of the disease process and/or care provided) (27). Several indicators are recommended to measure and improve the quality of care for this patient population, indicators that should be reliable and feasible to use, with clear and concise definitions (25). Among the criteria used, some authors advocate that patient outcomes, as in-hospital death defined in our study, should

be the standard and preferential criteria for assessing hospital quality. Ideally, multiple metrics will be needed to characterize hospital performance, depending and adjusted to the target population and the specifications of each institution.

Our study has some limitations. This is an observational and nonrandomized study. Data on potential contraindications to guideline recommendations and previously experienced untoward reactions to therapy were not collected, and both conditions may have influenced treatment choices and patient outcomes. Nevertheless, it should be noted that certain drugs are often not prescribed because of comorbidities, despite the available evidence of benefit in their presence. The prognostic impact of evidence-based care was assessed at the individual patient level, but practice patterns tend to cluster at the institutional level. Additionally, this study is focused on pharmacological therapies with prognostic impact, and does not assess compliance with respect to recommendations on the use of coronary angiography and myocardial revascularization, which are also known to modify outcomes when appropriate.

In conclusion, our study in a large population included in a national registry shows that current NSTEMI-ACS care is not perfect and guideline-based therapy is associated with improvement in hospital outcomes. In addition to several patient related-characteristics, process care and institutional related-variables influence the prognosis. Some of the patients with highest mortality risk were less likely to receive guideline-recommended therapies. These findings highlight the need to promote using the guideline and to develop approaches for quality improvement in this subset of patients. Although the improvement in guideline adherence over the last years, continuous quality assessment policies are needed to overcome the gap between evidence and practice.

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