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# Age and sex inequalities in the prescription of evidence-based pharmacological therapy following an acute coronary syndrome in Portugal: the EURHOBOP study

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## Abstract

**Aim:** To assess the proportion of patients receiving pharmacological therapy for secondary prevention after an acute coronary syndrome (ACS) in Portugal and to identify age and sex inequalities.

**Design:** Retrospective cohort study.

**Methods:** We studied 747 episodes of ST-segment elevation myocardial infarction (STEMI) and 1364 of non-ST-segment elevation ACS (NSTE-ACS), within a sample of ACS cases consecutively discharged from 10 Portuguese hospitals, in 2008–2009. We estimated adjusted odds ratios (OR) for the association of age and sex with the use of each pharmacological treatment.

**Results:** In STEMI and NSTE-ACS patients, the proportion of patients discharged with aspirin was 96 and 88%, clopidogrel 91 and 78%, aspirin+clopidogrel 88 and 71%, beta-blockers 80 and 76%, angiotensin-converting enzyme (ACE) inhibitors/ARB 82 and 80%, statins 93 and 90%, 3-drug (aspirin/clopidogrel+beta-blocker+statin) 76 and 69%, and 5-drug treatment (aspirin+clopidogrel+beta-blocker+ACE inhibitor/ARB+statin) 61 and 48%, respectively. Among STEMI patients, those aged ≥80 years were substantially less often discharged with clopidogrel (OR 0.22, 95% confidence interval, CI, 0.08–0.56), aspirin+clopidogrel (OR 0.34, 95% CI 0.15–0.76), beta-blockers (OR 0.39, 95% CI 0.18–0.82), 3-drug (OR 0.41, 95% CI 0.21–0.83), and 5-drug treatments (OR 0.44, 95% CI 0.23–0.83) than those <60 years; women were less likely to be discharged with aspirin+clopidogrel (OR 0.52, 95% CI 0.29–0.91). Among NSTE-ACS patients, those aged ≥80 years were much less likely to be discharged with beta-blockers (OR 0.58, 95% CI 0.36–0.93), statins (OR 0.35, 95% CI 0.19–0.64), and 3-drug treatment (OR 0.47, 95% CI 0.30–0.75); sex had no significant effect on treatment prescription.

**Conclusions:** The vast majority of younger patients were discharged on evidence-based secondary preventive medications, but only half received the 5-drug combination. Recommended therapies were substantially underprescribed in older patients.

## Keywords

Acute coronary syndrome, age, inequalities, secondary prevention, sex

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## Introduction

Ischaemic heart disease remains a leading cause of death worldwide and in Portugal.[1,2] Acute coronary syndrome (ACS) is the most prevalent manifestation of unstable ischaemic heart disease and can lead to

life-threatening complications after the acute phase. A combination of evidence-based secondary preventive medications and lifestyle interventions can substantially reduce that risk. However, these management strategies need to be considered and implemented at hospital discharge for all ACS survivors, regardless of age or sex.[3,4]

Age is associated with a higher risk of atherosclerotic diseases, due to the degenerative process associated with aging per se, together with the cumulative impact of the worsening risk-factor profile. In Portugal, the proportion of people aged over 65 years almost doubled from 1980 to 2010.[5] Patients with a first non-fatal ACS have an almost 10% risk of death within 6 months and advanced age is one of the most powerful independent predictors of death.[6] In 2000, 27% of the individuals admitted to public Portuguese hospitals with an acute myocardial infarction were aged over 75 years, while in 2008 this proportion increased to 35%.[7] Case fatality in these older patients is over twice that in those aged under 75 years.[6]

Women have traditionally been seen as a low-risk population for cardiovascular diseases. However, the incidence of cardiovascular diseases in women increases rapidly after menopause to levels similar to those observed in older men.[8] Thus in Portugal, in 2010, over 18,000 women and 15,000 men died from cardiovascular diseases.[9] Women now account for over one-third of acute myocardial infarction cases.[7] Furthermore, the age-adjusted prognosis after an ACS admission is worse in women than in men, possibly reflecting delays in diagnosis, more frequent atypical presentation, and crucially less aggressive treatment.[10]

Many studies have reported an underutilization of evidence-based treatment in ACS patients discharged from hospitals, particularly in women and older patients.[11,12] However, data on the use of pharmacological therapy after an ACS in Portugal are scarce.[13] Therefore, we analysed the proportion of patients receiving pharmacological therapy as secondary prevention after an ACS admission in 10 Portuguese hospitals, and explored potential age- and sex-differences.

## Methods

The EURopean HOspital Benchmarking by Outcomes in acute coronary syndrome Processes (EURHOBOP) project is a multicentre and multinational retrospective study of patients hospitalized with a final diagnosis of ACS, consecutively discharged from 70 hospitals in seven European countries (Finland, France, Germany, Greece, Italy, Portugal, and Spain). The current analysis only considers data from patients admitted in the 10 Portuguese hospitals.

The 10 hospitals were a convenience sample of public hospitals, selected to cover the mainland country from north to south and east to west, while serving both urban and rural populations. Participating hospitals are listed in the Supplementary Appendix (available online). Since we aimed to have hospitals with different levels of specialization represented in our sample, we invited hospitals with diverse characteristics, regarding facilities, infrastructure, and human resources' specialization. Overall, five hospitals had a catheterization laboratory, three had a cardiac surgery department, while one only had a general internal medicine department with no cardiology department or cardiologists; four were university hospitals; the number of beds ranged from 280 to 1124.

From each hospital, we obtained a series of 300 consecutive patients, independently of the departments where the patient had been hospitalized. The inclusion criteria were a discharge diagnosis of myocardial infarction, with or without ST-segment elevation, or unstable angina (International Classification of Diseases 10th revision: I21.0–I21.9 and I20.0). We aimed to study patients from 2009 but in hospitals whose annual number of cases was not enough to obtain the 300-patient sample we extended the recruitment period backwards to 2008.

The overall sample included a total of 3009 ACS patients. For this analysis, we excluded patients who died during hospitalization (8%), who were transferred to another hospital (11%), and patients with no data on discharge medication (9%) (Figure 1), leaving 2231 for analysis. In comparison with patients included in analysis, those without data on discharge medication were slightly older (median age 71 vs. 68 years, $p < 0.001$) and more frequently had a non-ST-segment elevation ACS (NSTE-ACS) (74.8 vs. 64.6%, $p = 0.003$). However, the proportion of men was identical (68.7 vs. 68.7%, $p = 0.552$).

Data was collected by trained medical record extractors using a standardized data collection form. The main source of information was the discharge letter, and information on emergency room records and laboratory information systems was accessed, whenever available. We extracted information on type of diagnosis, demographic characteristics, previous medical history, admission data, procedures used during hospitalization, severity indicators and complications during hospitalization, and discharge medication.

All drugs prescribed at discharge were recorded and classified according to the Anatomical Therapeutic Chemical Classification System (ATC). The discharge therapy considered for this analysis was aspirin (ATC code: B01AC06), clopidogrel (ATC code: B01AC04), beta-blockers (ATC codes: C07), angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor

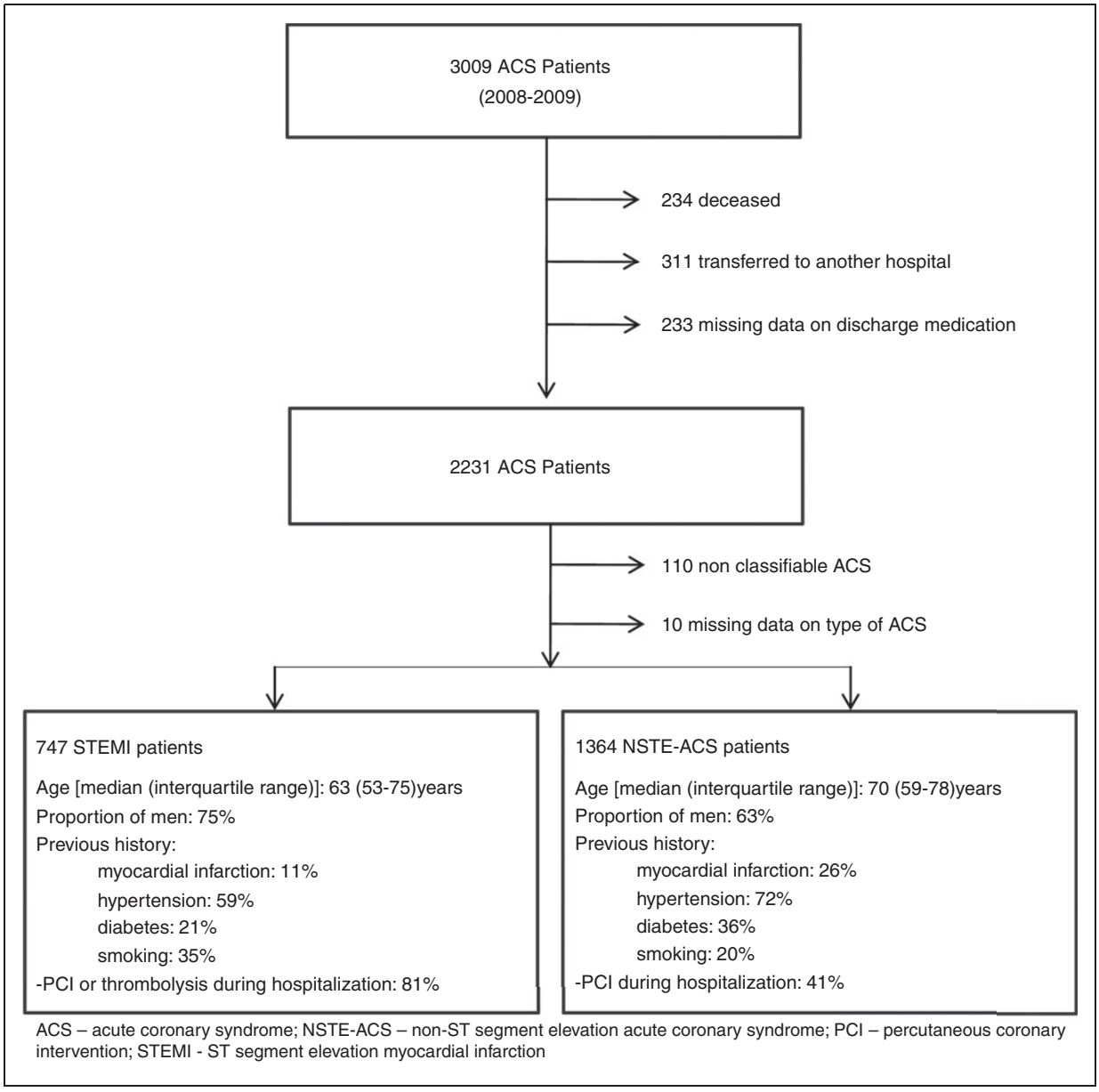


**Figure 1.** Flowchart illustrating the sample selection for the present analysis and the main characteristics of the patients, by type of acute coronary syndrome.

blockers (ARB) (ATC codes: C09A, C09B, C09C, and C09D) and statins (ATC codes: C10AA and C10BA). Additionally, we computed composite variables for drug combinations: double antiplatelet therapy with aspirin and clopidogrel, 3-drug treatment [(aspirin or clopidogrel) and beta-blocker and statin] and 5-drug treatment [aspirin and clopidogrel and beta-blocker and (ACE inhibitor or ARB) and statin].

We used mixed-effects logistic regression to estimate odds ratios (OR) for the association of age and sex with the use of each pharmacological treatment. The models included variables that are likely to influence the prescription due to their role as compelling indication or relative contraindication for each drug (see Table 1 footnotes) as fixed effects and random intercept at the hospital level to account for differences between hospitals. The potentially relevant confounders were identified based on previous knowledge, independently of their significant effect in this sample.[3,4] The main analysis presented in this paper was stratified by type of ACS: ST-segment elevation myocardial infarction (STEMI) or NSTE-ACS. Those who had non-classifiable type of ACS and missing data on that variable were excluded from this analysis. However, in

**Table 1.** Association between age and sex and the prescription of pharmacological treatment at discharge, among patients with acute coronary syndrome with or without ST-segment elevation

| | Aspirin[a] | Clopidogrel[a] | Aspirin and clopidogrel[a] | Beta-blocker[b] | ACEi/ARB[c] | Statin[d] | 3-drug treatment[e] | 5-drug treatment[f] |
|---|---|---|---|---|---|---|---|---|
| STEMI ($n=747$) | | | | | | | | |
| Age (years) | | | | | | | | |
| <60 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 60–79 | 1.05 (0.40–2.74) | 0.36 (0.16–0.81) | 0.58 (0.30–1.12) | 0.47 (0.28–0.79) | 1.14 (0.71–1.83) | 0.44 (0.20–0.94) | 0.45 (0.28–0.73) | 0.65 (0.42–0.99) |
| ≥80 | 0.59 (0.18–1.90) | 0.22 (0.08–0.56) | 0.34 (0.15–0.76) | 0.39 (0.18–0.82) | 0.77 (0.38–1.56) | 0.74 (0.26–2.15) | 0.41 (0.21–0.83) | 0.44 (0.23–0.83) |
| Sex | | | | | | | | |
| Men | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Women | 1.07 (0.43–2.65) | 0.54 (0.29–1.03) | 0.52 (0.29–0.91) | 1.09 (0.67–1.78) | 0.86 (0.53–1.39) | 1.19 (0.58–2.43) | 1.25 (0.79–2.00) | 0.74 (0.49–1.12) |
| NSTE-ACS ($n=1364$) | | | | | | | | |
| Age (years) | | | | | | | | |
| <60 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| 60–79 | 0.71 (0.43–1.16) | 0.93 (0.63–1.38) | 0.89 (0.62–1.28) | 0.83 (0.58–1.19) | 1.86 (1.33 –2.62) | 0.84 (0.49–1.43) | 0.86 (0.61–1.21) | 1.20 (0.87–1.64) |
| ≥80 | 0.94 (0.51–1.76) | 0.74 (0.46–1.20) | 0.78 (0.50–1.22) | 0.58 (0.36–0.93) | 1.46 (0.93–2.30) | 0.35 (0.19–0.64) | 0.47 (0.30–0.75) | 0.77 (0.50–1.20) |
| Sex | | | | | | | | |
| Men | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Women | 0.97 (0.67–1.41) | 0.93 (0.68–1.26) | 0.91 (0.68–1.22) | 1.14 (0.84–1.54) | 1.14 (0.84–1.56) | 0.79 (0.53–1.18) | 1.13 (0.85–1.51) | 0.96 (0.73–1.27) |

Values are adjusted odds ratio (95% CI). 3-drug treatment was defined as aspirin/clopidogrel+beta-blocker+statin; 5-drug treatment was defined as aspirin+clopidogrel+beta-blocker+ACEi/ARB+statin; [a]Adjusted for anaemia at admission, thrombolysis (only in STEMI patients), percutaneous coronary intervention, and atrial fibrillation; [b]Adjusted for previous history of smoking, bradycardia and hypotension at admission, thrombolysis (only in STEMI patients), percutaneous coronary intervention, heart failure, left ventricular dysfunction, renal failure, and atrial fibrillation; [c]Adjusted for previous history of diabetes and hypertension, bradycardia and hypotension at admission, thrombolysis (only in STEMI patients), percutaneous coronary intervention, heart failure, renal failure, and atrial fibrillation; [d]Adjusted for previous history of diabetes, thrombolysis (only in STEMI patients), percutaneous coronary intervention, and renal failure; [e]Adjusted for previous history of smoking and diabetes, bradycardia, hypotension and anaemia at admission, thrombolysis (only in STEMI patients), percutaneous coronary intervention, heart failure, left ventricular dysfunction, renal failure, and atrial fibrillation; [f]Adjusted for previous history of smoking, diabetes and hypertension, bradycardia, hypotension and anaemia at admission, thrombolysis (only in STEMI patients), percutaneous coronary intervention, heart failure, left ventricular dysfunction, renal failure, and atrial fibrillation; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction.

Supplementary Table 4 (available online) we report the effect of age and sex in all ACS patients, adjusting for the type of ACS, beyond other confounders.

The ethics committee of the University of Porto Medical School and the National Commission for Data Protection approved the study.

## Results

The median age of the 2231 patients was 68 years (range 21–99 years), and 20% were aged over 80 years. Approximately two-thirds were men (67%), with a lower median age than women (65 vs. 75 years). Fifty-two percent of the patients were submitted to a PCI and 1% to coronary artery bypass grafting surgery. Most patients were admitted with a NSTE-ACS (61%), while a third (33%) had a STEMI and nearly 5% had a non-classifiable type of ACS due to either subacute presentation or left bundle branch block of unknown duration. Information about the type of ACS was not reported in 0.5% of the patients' clinical files. Compared to the NSTE-ACS patients, those admitted with STEMI were younger and more frequently males and smokers, but less frequently hypertensive or diabetic and had a lower prevalence of previous myocardial infarction (Figure 1).

Overall, at discharge, 91.0% of patients had a prescription of aspirin, 81.5% clopidogrel, 76.5% both aspirin and clopidogrel, 77.6% a beta-blocker, 80.0% an ACE inhibitor/ARB, 91.3% a statin, 71.4% the 3-drug treatment, and 51.8% the 5-drug treatment.

Among those with a diagnosis of STEMI, 96.2% of patients were discharged with aspirin, 91.0% clopidogrel, 88.5% both aspirin and clopidogrel, 80.5% a beta-blocker, 81.9% a ACE inhibitor/ARB, 93.3% a statin, 75.6% the 3-drug treatment, and 61.2% the 5-drug treatment. The corresponding proportions for NSTE-ACS patients were consistently lower: 88.1% aspirin, 77.7% clopidogrel, 71.4% both aspirin and clopidogrel, 76.2% a beta-blocker, 79.0% a ACE inhibitor/ARB, 90.3% a statin, 69.5% for the 3-drug treatment and 47.9% for the 5-drug treatment.

Considering only patients with a first ACS the proportions were very similar, except for a marginally significant difference in clopidogrel use in STEMI patients (85.0 vs. 91.8%, in patients with and without previous myocardial infarction, respectively, $p = 0.05$).

Overall, the proportion of patients discharged with pharmacological treatments was higher in younger patients for almost all medications (Figure 2, left hand panel). We observed a difference of more than 20% between the youngest and the oldest patients (<60 vs. ≥80 years) in the proportion of STEMI patients treated with aspirin and clopidogrel (94.2 vs. 72.9%), 3-drug treatment (84.5 vs. 61.5%), and 5-drug treatment (84.5 vs. 61.5%). Similar differences were noted among NSTE-ACS patients for clopidogrel (85.7 vs. 62.6%), aspirin and clopidogrel (81.2 vs. 55.5%), 3-drug treatment (76.1 vs. 55.9%), and 5-drug treatment (53.9 vs. 31.5%). The sex differences were smaller than those observed with age (Figure 2,

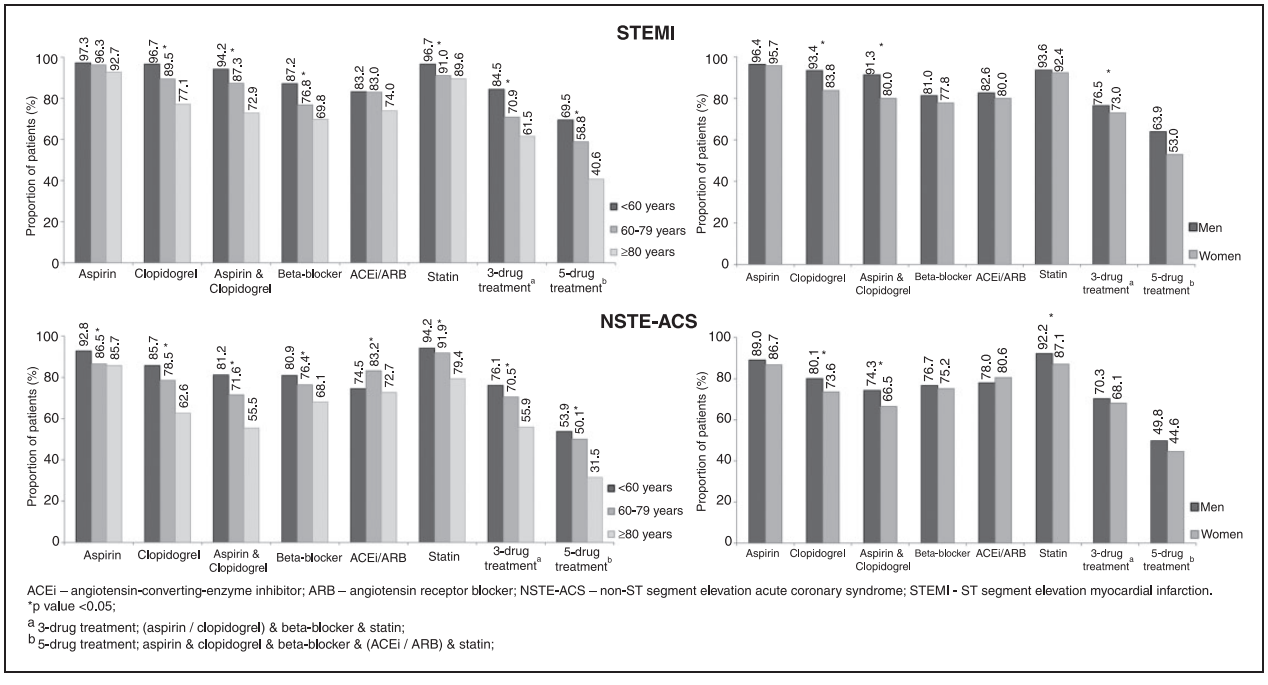


**Figure 2.** Proportion of patients discharged with pharmacological treatment after an acute coronary syndrome with or without ST-segment elevation according to age (left) and sex (right).

right hand panel). Women were significantly less likely to receive clopidogrel, aspirin and clopidogrel, and 5-drug treatment, among STEMI patients; and clopidogrel and statins, among NSTE-ACS patients.

Table 1 presents the independent associations between age and sex and the use of each pharmacological treatment. The detailed tables presenting the OR for all variables included in the final models are presented in the Supplementary Appendix. Among STEMI patients, women were much less likely to be discharged with aspirin and clopidogrel (OR 0.52). Compared to patients aged under 60 years, those aged over 80 years were far less often discharged with clopidogrel (OR 0.22), aspirin and clopidogrel (OR 0.34), beta-blockers (OR 0.39), statins (OR 0.74), 3-drug treatment (OR 0.41), and 5-drug treatment (OR 0.44). Among NSTE-ACS patients, patients ≥80 years were less likely to be discharged with beta-blockers (OR 0.58), statins (OR 0.35), and 3-drug treatment (OR 0.47), comparing with patients aged <60 years. There were no significant sex differences in pharmacological treatment prescribing among NSTE-ACS patients.

When considering only patients with a first ACS, the independent associations between age and sex and the use of each pharmacological treatment were very similar, in both STEMI and NSTE-ACS patients.

## Discussion

We report a large sample of consecutive ACS patients discharged from 10 Portuguese representative hospitals across 2008 and 2009. A large majority of these patients were discharged with the main evidence-based pharmacological treatments. However, only half received the recommended 5-drug treatment. Worse still, increasing age had an independent and powerful adverse effect on the proportion of patients discharged on effective therapies.

Approximately 10% of post-ACS patients have a recurrent event within a year after discharge and mortality after discharge remains relatively high.[14] However, pharmacological secondary prevention is potentially very effective in improving these outcomes, but only if prescribed.[3,4] Decisions on how to manage individual patients should be based on existing recommendations, taking into account the possible contraindications and cautions warranted for each treatment, as well as possible drug interactions. There is a powerful international consensus that, after having considered contraindications, all ACS patients should be discharged on low-dose aspirin, an oral adenosine diphosphate receptor antagonist, a beta-blocker, and a lipid-lowering drug.[3,4] Furthermore, although the use of ACE inhibitors in all ACS patients is not unanimously accepted,[15] the current European guidelines clearly recommend their prescription at discharge for all patients.[3,4]

Despite the universal acceptance of clinical guidelines and management tools for ACS, there are geographic variations in the management of ACS.[16] Several studies have reported the proportion of ACS patients discharged with pharmacological treatment in European countries, and in general these proportions were high.[16] Estimates from the Euro Heart Survey, an European programme that included data from 22 countries and in which Portugal did not participate, reported that 91% of the ACS patients were discharged with antiplatelet drugs, 80% with beta-blockers, 71% with ACE inhibitors, and 78% with statins, at hospital discharge, in 2006–2007.[16] However, the proportions obtained in most of the existing registries may be overestimates, since they may represent higher risk patients, admitted in cardiology departments, in urban or teaching hospitals with cardiac intensive care units. For instance in Portugal, the National Registry of Acute Coronary Syndromes suggested that between 2002 and 2008, approximately 94% of ACS patients were discharged with aspirin, 52% with aspirin and clopidogrel, 71% with beta-blockers, 71% with ACE inhibitors, 87% with statins, and 63% with the combination of aspirin, clopidogrel, beta-blockers, ACE inhibitors, and statins.[13] Our data cannot be directly compared with those estimates, since that registry only covers cardiology departments, it does not assure the consecutiveness of patients within participating centres and generates estimates not necessarily representative for age or sex.

In contrast, the diverse settings covered in our study potentially offer better representativeness of the general ACS population. Furthermore, the large consecutive sample of cases within a narrow time span regardless of the department where they had been hospitalized provides potentially important new data. Also, the sample provided unique data on the confounders of age and sex. While treatment with invasive procedures may be dependent on hospital facilities such as a catheterization laboratory, the prescription of pharmacological treatment at discharge only depends on the medical decision. Thus, any variation in treatment that persisted after adjusting for the wide range of confounders was likely to reflect true inequalities.

Despite the prescription of pharmacological treatment to the vast majority of patients at discharge, there is still scope for considerable improvement.[17] In order to achieve optimal treatment it is particularly important to identify which groups of patients are being undertreated and the underlying reasons.

The major differences according to age suggest that physicians remain reluctant to prescribe these post-ACS medications to older patients,[18,19] despite the

strong evidence that the old and very old would obtain a particularly large absolute benefit.[20,21] The general belief that the elderly are at higher risk of side effects from pharmacological treatment, such as bleeding with antiplatelet agents and anticoagulants, hypotension, bradycardia, and renal failure, may partly explain the under-prescription of these drugs in this population. We assessed the effect of age independently of the main contraindications or variables with a possible role as compelling indication, and older patients were undertreated even after adjustment. Despite previous reports highlighting the need to address age-dependent inequalities in the quality of care for ACS,[22–24] elderly patients hospitalized with an ACS continue to be disadvantaged when compared with younger patients. These persistent inequalities argue for future studies of motives and perceived barriers in using these evidence-based treatments, including a comparison between real and perceived clinical contraindications.

Although most therapeutic guidelines explicitly state that both sexes should be evaluated and treated in the same way, women with ACS have been less likely than men to receive evidence-based treatment in some populations.[25,26] Women with an ACS diagnosis are more likely to be older than men and to have diabetes, hypertension, heart failure, or other comorbidities.[27,28] This might perhaps justify part of the observed differences. Fortunately, our study suggests some improvements. We observe very few sex-differences in discharge medications after adjusting for the potential confounding effect of age, comorbidities, and contraindications.

This was the first study to examine treatments after ACS including consecutive patients recruited in a large sample of Portuguese hospitals, from whom only 11% were transferred to other hospitals. To compute the independent effect of age and sex, we considered the main confounding variables at the individual level and the effect of the hospital, using a hierarchical approach. However, some limitations need to be acknowledged. Given the retrospective nature of this study, the validity of the conclusions relies on the accuracy and completeness of the original documentation. Although we had information for the most important variables to address our objectives, we must recognize that it would be best to have a better characterization of patient's socioeconomic position and other clinical information (for instance, peptic ulcer, and previous experience with these drugs in the same patient). It is important to note that this study did not examine the appropriateness of dosage or adherence rates and, therefore, no inference can be made on these issues. Patient's adherence to medications was not assessed, but our primary focus was on physicians' prescription patterns, and their compliance to guidelines. In addition to pharmacological treatment, lifestyle changes are important in secondary prevention.[3,4] Since this information was not described systematically in the original documentation, we were not able to assess the extent to which this recommendation was given to the patients. Finally, we had missing data on discharge medication in 9% of the study population, and those excluded were significantly older and more frequently had a NSTE-ACS diagnosis, when compared with the patients with information on discharge medication. This suggests that the proportions reported are slightly overestimated when comparing with the initial sample selected for this study.

In conclusion, the vast majority of patients received evidence-based pharmacological treatment, but only half were discharged with the combination of the recommended five drugs. Further improvements are necessary, especially in elderly patients, in order to reduce future events and to improve their quality of life.

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## Conflict of interest

The authors declare that there is no conflict of interest.

## Acknowledgements

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