ДРУЖЕСТВО НА КАРДИОЛОЗИТЕ В БЪЛГАРИЯ
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THE PROGNOSTIC IMPACT OF COMPLETE REVASCULARIZATION DURING HOSPITALIZATION IN NON-ST ELEVATION MYOCARDIAL INFARCTION – ANALYSIS FROM THE REAL-LIFE PORTUGUESE REGISTRY FOR ACUTE CORONARY SYNDROMES

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ПРОГНОСТИЧНОТО ВЪЗДЕЙСТВИЕ НА ПЪЛНАТА РЕВАСКУЛАРИЗАЦИЯ ПО ВРЕМЕ НА ХОСПИТАЛИЗАЦИЯ ПРИ МИОКАРДЕН ИНФАРКТ БЕЗ ST-ЕЛЕВАЦИЯ – АНАЛИЗ ОТ РЕАЛНИ ПОРТУГАЛСКИ РЕГИСТЪР ЗА ОСТРИ КОРОНАРНИ СИНДРОМИ

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Abstract. **Introduction and objectives:** Multivessel disease (MVD) occurs in approximately half of non–ST elevation myocardial infarction (NSTEMI) patients and is associated with an increased risk of cardiovascular events. However, current recommendation for complete revascularization in NSTEMI is based in observational and non-randomized studies suggesting a possible benefit regarding mortality and major cardiovascular events. This study aimed to retrospectively evaluate the prognostic impact of complete percutaneous revascularization in a population of patients with NSTEMI and MVD. **Material and methods:** This was a national multicentre retrospective study of patients hospitalized for NSTEMI with MVD, included on the Portuguese Registry for Acute Coronary Syndromes (ProACS). The impact of complete percutaneous revascularization on in-hospital and one-year mortality rates, as well as on the probability of cardiovascular re-hospitalization was evaluated. **Results:** A total of 3084 patients were included in this analysis. We found no significant differences between groups regarding in-hospital complications and mortality, as well as median hospitalization length. Nevertheless, complete revascularization showed a significant impact on the primary endpoint of all-cause mortality or cardiovascular re-hospitalization (11.9% vs. 20.4%, p < 0.001), mainly driven by a major reduction in unplanned cardiovascular re-hospitalizations at one year of follow-up (9.3 vs. 16.8%, p < 0.001). Conversely, one-year mortality rate was once again similar between groups (4.2 vs. 5.0%, p = 0.536). **Conclusions:** In our population, complete revascularization during hospitalization was associated with lower risk of the primary endpoint of all-cause mortality or cardiovascular re-hospitalization, mainly driven by a major reduction in cardiovascular re-hospitalizations, with similar rate of intra-hospital complications.

Key words: non-ST elevated myocardial infarction; coronary artery disease; percutaneous coronary intervention; myocardial revascularization

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Резюме. **Въведение и цел:** Многосъдовата болест (МСБ) се среща при приблизително половината от пациентите с миокарден инфаркт без ST-елевация (NSTEMI) и е свързана с повишен риск от сърдечно-съдови събития. Въпреки това настоящите препоръки за пълна реваскуларизация при NSTEMI се основават на наблюдателни и нерандомизирани проучвания, които предполагат възможна полза по отношение на смъртността и сериозните сърдечно-съдови събития. Целта на това проучване е да оцени ретроспективно прогностичното въздействие на пълната перкутанна реваскуларизация при популация пациенти с NSTEMI и МСБ. **Материал и методи:** Това е национално многоцен-

трово ретроспективно проучване на пациенти, хоспитализирани за NSTEMI и с МСБ, включени в Португалския регистър за остри коронарни синдроми (ProACS). Оценено е влиянието на пълната перкутанна реваскуларизация върху смъртността в болницата и в рамките на една година след това, както и върху вероятността от повторна хоспитализация поради сърдечно-съдови причини. **Резултати:** В анализа са включени общо 3084 пациенти. Не са установени значими разлики между групите по отношение на вътреболничните усложнения и смъртността, както и относно средната продължителност на хоспитализацията. Въпреки това пълната реваскуларизация показва значително влияние върху първичната крайна точка за смъртност от всички причини или повторна хоспитализация поради сърдечно-съдови причини (11,9% спрямо 20,4%, p < 0,001), главно поради значително намаление на непланираните повторни хоспитализации по сърдечно-съдови причини при едногодишно проследяване (9,3 спрямо 16,8%, p < 0,001). От друга страна, едногодишната смъртност отново е сходна между групите (4,2% спрямо 5,0%, p = 0,536). **Заключение:** В нашата популация пълната реваскуларизация по време на хоспитализацията беше свързана с по-нисък риск по отношение на първичната крайна точка – смъртност по всички причини или повторна хоспитализация поради сърдечно-съдови причини, главно благодарение на значителното намаление на рехоспитализациите поради сърдечно-съдови причини, при сходна честота на вътреболнични усложнения.

Ключови думи: инфаркт на миокарда без ST-елевация; коронарна артериална болест; перкутанна коронарна интервенция; реваскуларизация на миокарда

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Introduction

Multivessel disease (MVD) is evident in approximately half of non-ST-elevation myocardial infarction (NSTEMI) patients and is associated with an increased risk of cardiovascular events [1-3].

Complete revascularization in NSTEMI was proved safe, with comparable rates of in-hospital mortality, bleeding, renal failure and non-fatal cardiogenic shock to culprit-only revascularization (4) Nevertheless, while numerous recent randomized trials have provided robust evidence supporting complete percutaneous revascularization for ST-elevation acute myocardial infarction concerning hard endpoints [3, 5-10], there is a noticeable lack of studies assessing its prognostic impact in NSTEMI. In fact, the current recommendation for complete revascularization in NSTEMI [11] is based primarily in observational and non-randomized studies suggesting a possible benefit regarding mortality and major cardiovascular events [1, 12].

This study, therefore, aimed to assess the prognostic impact of complete revascularization in a Portuguese population with NSTEMI and MVD.

Material and methods

This was a national multicentre retrospective study of patients hospitalized for NSTEMI with MVD. Data was collected from the Portuguese Registry for Acute Coronary Syndromes (ProACS). Patients are enrolled on the ProACS during hospitalization for ACS, on a voluntary basis, by signing a written informed consent form.

The ProACS is a national multicentre continuous prospective observational registry, coordinated by the National Centre for Data Collection in Cardiology under the aegis of the Portuguese Society of Cardiology. All cardiology departments at Portuguese hospitals were invited to consecutively include adult patients hospitalized for ACS. Collected data include demographic and clinical characteristics, laboratory test results, clinical course, treatment (medical and interventional), as well as data regarding vital status and hospitalizations at one-year follow-up. The registry was approved by the Portuguese Data Protection Authority (no. 3140/2010), is registered at ClinicalTrials.gov (NCT 01642329), and is supervised by an Executive Committee appointed for this purpose [13].

In this analysis, all 14 892 NSTEMI patients consecutively enrolled between October 2010, and December 2022 were considered. For all patients, relevant demographic and previous clinical data, NSTEMI related data (including clinical data, medical and interventional treatments, and complications), vital status and therapy at discharge, as well as vital status and re-hospitalization data at one-year of follow-up were available. Those with missing data regarding coronary angiography or revascularization, or who were not submitted to invasive coronary angiography during admission, were excluded.

MVD was defined as the presence of at least 50% diameter stenosis in angiography of at least one non-culprit artery. The culprit lesion was identified as the coronary stenosis associated with the presentation of ACS based on clinical, non-invasive, or invasive data. We defined two-vessel disease as the presence of at least 50% diameter stenosis in angiography in one non-culprit artery and three vessel-disease in two non-culprit arteries.

Complete revascularization was defined as percutaneous coronary intervention of all coronary arteries

with angiographic ≥ 50% diameter stenosis. This could be done either during the initial procedure or staged throughout the remaining hospitalization, depending on the operator's judgment.

Patients were categorized into two groups based on the revascularization strategy: one group that underwent complete percutaneous revascularization during the index hospitalization and another one who received incomplete revascularization. The primary endpoint was one-year all-cause mortality or cardiovascular re-hospitalization (which included hospitalization for unplanned revascularization, heart failure decompensation or ventricular arrhythmias excluding elective or planned procedures). Secondary endpoints included in-hospital complications and mortality.

Statistical analysis

Categorical variables were expressed as frequencies and percentages and were compared using the chi-square test. Continuous variables were presented as mean and standard deviation (for normal distribution) or median and interquartile range (IQR) (the ones without normal distribution). Comparisons between groups were conducted with independent samples t-test or non-parametric tests. Kaplan-Meier curves were used to assess one-year survival differences according to complete or incomplete revascularization, and the difference was assessed by the log rank test. Statistically significant differences were assumed when the p-value was < 0.05. IBM SPSS Statistics version 25 (IBM, Armonk, New York) was used for the statistical analysis.

Results

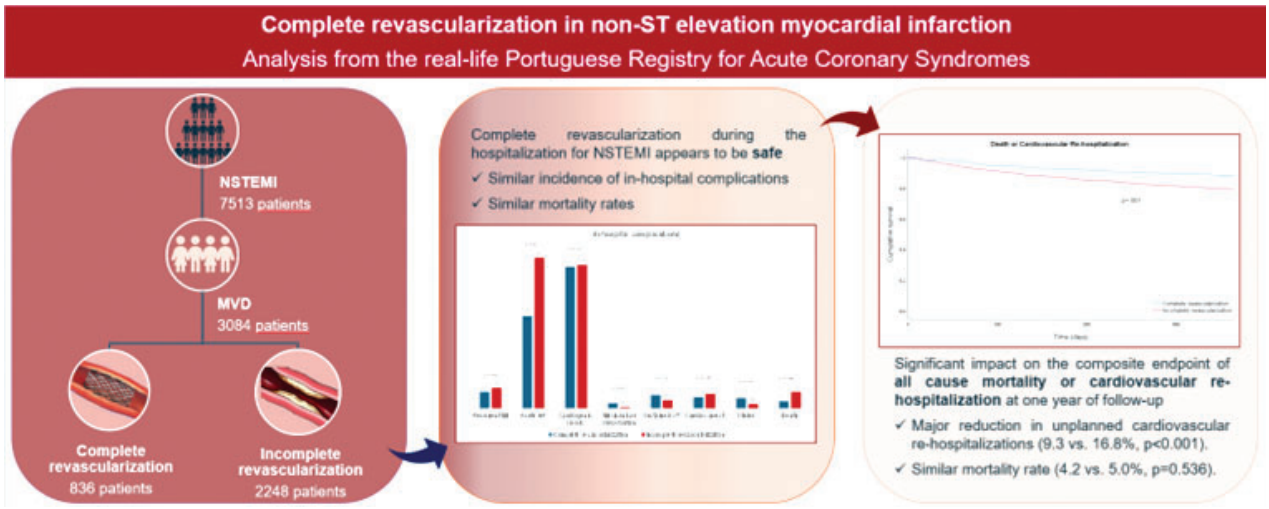
Among the 7513 NSTEMI patients with coronary angiography data in the ProACS registry, a total of 3084 (41.0%) presented MVD and were included in this analysis (central illustration). Most participants were males (74.8%) with a mean age of 67.8 ± 11.9 years. The majority of our patients was submitted to incomplete revascularization (72.9%). Among those who received complete revascularization, 81.4% had it performed during the index procedure, while 18.6% had it staged during the remaining hospitalization.

Baseline characteristics and comparisons between groups are presented in Table 1. Patients who received complete revascularization were younger (65.5 ± 11.8 vs. 68.6 ± 11.8 years, p < 0.001) and had fewer cardiovascular risk factors, except for smoking and obesity. Conversely, those who had incomplete revascularization exhibited a significantly higher prevalence of comorbidities, namely chronic kidney disease (9.1 vs. 4.8%, p < 0.001), stroke (9.5 vs. 5.9%, p = 0.002), peripheral artery disease (7.9 vs. 5.7%, p = 0.037) and valvular heart disease (3.6 vs. 1.6%, p = 0.005). They also had a higher incidence of previous acute myocardial infarction (31.7 vs. 17.1%, p < 0.001) and percutaneous or surgical revascularization (21.9 vs. 17.4%, p = 0.007 and 14.8 vs. 1.6%, p < 0.001).

In-hospital evolution

The majority of patients presented to the emergency department in Killip class I (85.2%) and with 180 minutes of symptoms (IQR 98-402). Notably, those presenting in higher Killip classes, including patients with cardiogenic shock (0.8%), as well as those with reduced left ventricular ejection fraction were less likely to receive complete revascularization (9.7 vs. 16.8%, p < 0.001 and 22.5 vs. 35.5%, p < 0.001) (Table 2).

Coronary angiography identified two-vessel disease in 57.5% of the patients, while the remaining



Central illustration: Study population, in-hospital and one-year follow-up results for the comparison of complete versus incomplete revascularization in patients with non-ST elevation myocardial infarction and multivessel disease. MVD – multivessel disease; NSTEMI – non-ST elevation myocardial infarction

Table 1. Baseline characteristics according to the revascularization strategy

	Complete revascularization (N = 836)	Incomplete revascularization (N = 2248)	p-value
Male	613 (73.3)	1694 (75.4)	0.248
Age (years)	65.5 ± 11.8	68.6 ± 11.8	< 0.001
Previous MI	141 (17.1)	700 (31.7)	< 0.001
Previous PCI	144 (17.4)	486 (21.9)	0.007
Arterial hypertension	601 (72.5)	1762 (79.5)	< 0.001
Diabetes mellitus	298 (36.2)	935 (42.1)	0.003
Dyslipidaemia	494 (61.1)	1443 (66.7)	0.004
Smoking	239 (28.6)	482 (21.4)	< 0.001
Obesity	207 (27.6)	545 (28.2)	0.727
Stroke	49 (5.9)	211 (9.5)	0.002
Peripheral artery disease	47 (5.7)	175 (7.9)	0.037
Heart failure	43 (5.2)	153 (6.9)	0.091
Valvular heart disease	13 (1.6)	79 (3.6)	0.005
Chronic kidney disease	40 (4.8)	201 (9.1)	< 0.001

Table 2. In-hospital outcomes according to the revascularization strategy

	Complete revascularization (N = 836)	Incomplete revascularization (N = 2248)	p-value
Killip class > I	81 (9.7)	372 (16.8)	< 0.001
Left ventricular ejection fraction	55 ± 11	51 ± 11	< 0.001
Serum creatinine > 2 mg/dL at presentation	36 (4.5)	147 (6.9)	0.459
Maximum serum creatinine > 2 mg/dL	55 (8.4)	240 (13.3)	0.668
Baseline angiographic analysis			
Two vessel disease	699 (83.6)	1073 (47.7)	< 0.001
Three vessel disease	137 (16.4)	1175 (52.3)	< 0.001
Stenosis ≥ 50%			
Left main	62 (7.6)	236 (11.2)	0.004
Left anterior descending	641 (76.8)	1972 (85.8)	< 0.001
Left circumflex	604 (72.4)	1773 (79.2)	< 0.001
Right coronary artery	498 (59.6)	1878 (64.1)	< 0.001
In-hospital complications			
Recurrent MI	13 (1.6)	44 (2.0)	0.456
Acute HF	74 (9.0)	326 (14.7)	< 0.001
Cardiogenic shock	12 (13.8)	52 (14.0)	0.957
Mechanical complication	4 (0.5)	3 (0.1)	< 0.001
Sustained VT	11 (1.3)	18 (0.8)	0.191
Cardiac arrest	9 (1.1)	31 (1.4)	0.505
Stroke	8 (1.0)	8 (0.4)	< 0.001
Death	6 (0.7)	36 (1.6)	0.060

Baseline characteristics are represented as N (%) or mean ± standard deviation. HF – heart failure; MI – myocardial infarction; VT – ventricular tachycardia

42.5% presented three-vessel disease. Complete revascularization was less frequent in patients with three-vessel disease (16.4 vs. 52.3%, p < 0.001).

Considering in-hospital complications (Fig. 1), patients submitted to complete revascularization exhibited less rates of acute heart failure (9,0% vs 14,7%, p < 0,001), mechanical complications (0,5% vs 0,1%, p < 0,001), or stroke (1,0% vs 0,4%, p = 0,51) during hospitalization, as well as a non-significant trend to an inferior in-hospital mortality rate (0.7 vs. 1.6%, p = 0.06). However, they presented with similar rates of recurrence of acute myocardial infarction (1.6 vs. 2.0%, p = 0,456).

The median hospitalization length was not significantly affected by the revascularization strategy [4 (2; 6) vs. 5 (2.5; 10) days, p = 0.396].

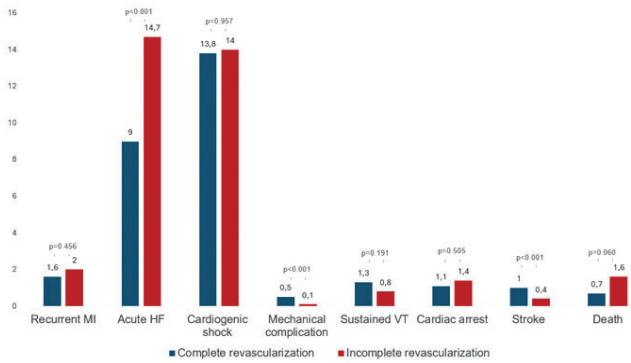


Fig. 1. In-hospital complications according to the revascularization strategy

Follow-up

After one year of follow-up, complete revascularization showed a significant impact on the primary endpoint of all-cause mortality or cardiovascular re-hospitalization with rates of 11.9% compared to 20.4% in the incomplete revascularization group (p < 0.001) (Fig. 2).

However, when analysing its individual components, it becomes evident that this benefit primarily arises from a major reduction in unplanned cardiovascular re-hospitalizations at one year of follow-up (9.3 vs. 16.8%, p < 0.001). Conversely, one-year mortality rate was once again similar between groups (4.2 vs. 5.0%, p = 0.536).

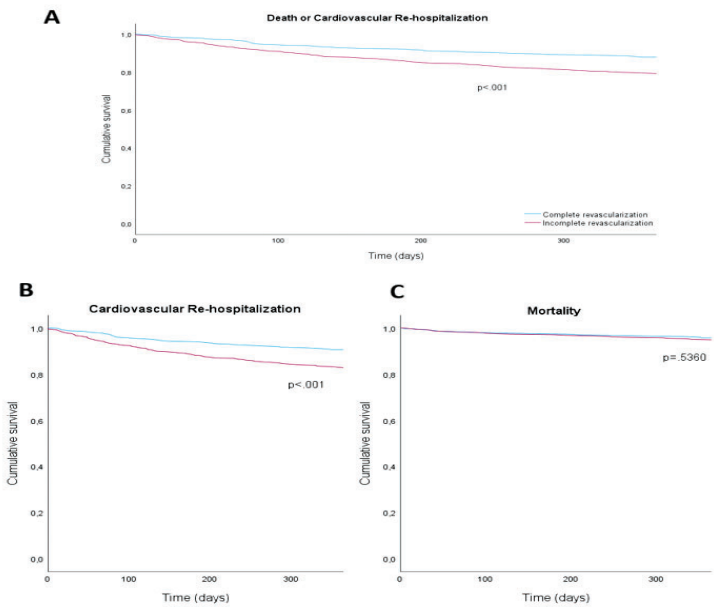


Fig. 2. Kaplan-Meier curves showing reduction of Primary endpoint of death or cardiovascular re-hospitalization (Panel A), mainly driven by a reduction in unplanned cardiovascular re-hospitalizations (Panel B), without a significant impact on one-year mortality rate (Panel C)

Discussion

The main findings of this national registry analysis are threefold. First, complete revascularization in NSTEMI patients with multivessel disease was associated with significantly lower rates of the composite endpoint of all-cause mortality or cardiovascular re-hospitalization at one year, mainly driven by a reduction in unplanned cardiovascular hospitalizations. Second, in-hospital complications and mortality were similar between complete and incomplete revascularization, supporting the safety of this strategy. Third, complete revascularization was less frequently achieved in patients with more complex coronary anatomy or hemodynamic instability, such as those with three-vessel disease or higher Killip class.

These results highlight that, even in real-world practice and despite the inclusion of patients with less severe lesions, complete revascularization may provide a prognostic benefit by reducing recurrent hospitalizations, without increasing short-term procedural risk.

MVD is observed in a substantial proportion of NSTEMI patients [1-3]. In our study, its prevalence was 41.0%, which is consistent with the described in previous literature [12]. While the benefits of complete revascularization are well-established for STEMI [5-10], its role in NSTEMI remains a matter of debate, due to the scarcity of randomised trials comparing different revascularization strategies. To our knowledge, this work is among the largest modern registries that compare complete and incomplete percutaneous revascularization strategies in NSTEMI patients with MVD.

As noted by Brener SJ et al. [4] complete revascularization during the hospitalization, for NSTEMI appears to be safe, as evidenced in our study by similar in-hospital complications and mortality rates between the two groups.

Unlike previous studies [12, 14], in our analysis, complete revascularization was not associated with a reduction in one-year all-cause mortality. This discrepancy might be at least partially attributed to the severity of the coronary lesions, which were considered significant and, thus, with indication for revascularization if there was at least 50% stenosis of the coronary lumen. However, according to the most recent guidelines [15], a visually estimated diameter stenosis of at least 70%, or 50% for left main disease, should be regarded as significant. In fact, in the FAME (Fractional Flow Reserve versus Angiography for Multivessel Evaluation) trial [16], only 35% of the 50-70% stenoses were found to be haemodynamically relevant. Therefore, using broader criteria may have resulted in the inclusion of less severe lesions, which would not have such prognostic relevance.

Complete revascularization was less frequent among patients with three-vessel disease (16.4 vs. 52.3%, p < 0.001). This may be due to the more complex nature of their disease, which may not be amenable for percutaneous revascularization. The presence of multiple significant stenosis allied to the potential overestimation lesion severity during the acute phase of the NSTEMI might also difficult the prompt identification of the culprit lesion, which may remain unidentified in up to 51% of the patients [12]. Additionally, the possible presence of chronic total occlusions could not be ruled-out and may have affected not only the revascularization strategy, but also the prognosis of such patients.

Less stable patients, such as those presenting in higher Killip classes or with reduced left ventricular ejection fraction were also less likely to receive complete revascularization.

Nevertheless, even for less severe lesions, complete revascularization did in fact associate with an improved one-year prognosis, by virtually halving the incidence of unplanned cardiovascular re-hospitalizations.

These findings support a more comprehensive revascularization approach in NSTEMI patients with multivessel disease, provided anatomical and hemodynamic conditions allow it. Reducing recurrent hospitalizations may translate into improved quality of life and lower healthcare burden. Future randomized studies should confirm whether these benefits persist with stricter anatomical and physiological lesion assessment.

The present work as, however, some limitations. First of all, this was an observational retrospective study of patients from the ProACS registry, in which the inclusion of each patient is voluntary and depends on their informed consent. Consequently, limitations inherent to observational non-randomized studies apply. There may also exist some differences between the institutions participating in the Registry, potentially introducing selection bias. However, a relatively large number of patients was included in the analysis, thus constituting a representative picture of the Portuguese reality. Although observational studies may only arrant hypothesis generation, in the absence of randomized controlled trials evaluating the prognostic impact of complete revascularization in NSTEMI patients, such population-based studies can still offer valuable insights for clinical practice.

Secondly, the presented data were sourced from a multicentre registry, without a “core lab” to adjudicate events. More detailed information on the cause of death or cardiovascular hospitalization at one-year was not available. Also, being a retrospective observational study, differences in patient baseline characteristics might had some impact on the results obtained.

Third, as previously mentioned, coronary lesions with angiographic stenosis of at least 50% were considered significant. This broad criterion might have led to the inclusion of less severe patients, impairing the evaluation of the prognostic impact in hard outcomes such as one-year mortality. A more stringent definition of angiographically significant lesions, even incorporating intracoronary imaging or functional analysis, might help to better select patients who would benefit the most of this strategy. Additionally, an analysis of the exact extent and location of the coronary lesions might be of interest, since distal or smaller vessel lesions may not have the same prognostic importance than proximal dominant vessels stenosis. Operator preferences could result to culprit-vessel only revascularization in cases of hemodynamic instability or complicated procedures.

Conclusion

This national multicentre study stressed the importance of a complete revascularisation in NSTEMI patients with MVD. Complete revascularization led to an overall long-term benefit, mainly due to a major reduction in cardiovascular re-hospitalizations, without a significant impact on one-year mortality rate. Further randomized controlled trials are needed to validate these findings.

Ethics Statement: The study was conducted in accordance with the principles outlined in the Declaration of Helsinki. The registry was approved by the Portuguese Data Protection Authority (no. 3140/2010), is registered at ClinicalTrials.gov (NCT 01642329), and is supervised by an Executive Committee appointed for this purpose. Patients are enrolled on the ProACS during hospitalization for ACS, on a voluntary basis, by signing a written informed consent form.

Conflict of Interest: The authors declare no conflicts of interest related to this manuscript.

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Data Sharing Statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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