

Editorial

Medically–managed Patients With Non–ST-segment Elevation Acute Coronary Syndromes: An Ill-defined Entity



Tratamiento conservador en pacientes con síndrome coronario agudo sin elevación del ST: una entidad mal definida

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Early coronary angiography followed by coronary revascularization, if appropriate, is the recommended management for most patients presenting with non–ST-segment elevation acute coronary syndrome (NSTEMI). While the outcomes of patients undergoing (usually percutaneous) coronary revascularization have been extensively described, the characteristics and outcomes of patients not undergoing coronary angiography or treated conservatively after a coronary angiogram are less well defined. From this perspective, Bueno et al.¹ sought to investigate the outcomes of NSTEMI patients medically managed (compared with those who have undergone coronary revascularization) in the EPICOR (long-term follow-up of antithrombotic management Patterns In acute CORonary syndrome patients) study. EPICOR was a prospective international registry, which enrolled 10 568 acute coronary syndrome patients (with both ST-segment elevation and NSTEMI) at the time of hospital discharge who were followed up for 2 years. Patients were enrolled in Northern, Southern, and Eastern Europe as well as Latin America between September 2010 and March 2011. Among 5591 NSTEMI patients included, 2306 (41.2%) did not undergo coronary revascularization and were defined by the authors as the medical management group. These patients belonged to 3 different entities: a) patients who did not undergo coronary angiography (CAG–) (n = 1186 [21.2%]); b) patients who did undergo coronary angiography, which showed no significant coronary artery disease (CAG+CAD–) (n = 451 [8.1%]); c) patients who did undergo coronary angiography, depicting significant coronary artery disease, but who did not undergo coronary revascularization (CAG+CAD+) (n = 669, [12%]). Significant coronary artery disease was defined as the presence of at least 1 artery with > 50% stenosis, although the investigators mentioned that the cutoff of 70% stenosis to define significant coronary artery disease would have not significantly change the results of the study (data not shown by the investigators).

Unsurprisingly, 2-year mortality was higher in medically managed than in revascularized patients (11.0% vs 4.4%, respec-

tively; $P < .001$). Among medically managed patients, the lowest mortality was observed in CAG+CAD– patients (4.1%), followed by the CAG+CAD+ group (9.3%), while CAG– patients had the highest mortality (14.6%) ($P = .001$). Obviously, the 3 patient populations composing the medical management group differed substantially. With respect to baseline characteristics, significant differences were observed for virtually all parameters, and most of the differences were driven by CAG+CAD– patients who were at lower risk. Taking as a reference those patients undergoing coronary revascularization and after adjustment for EPICOR risk score covariates, CAG+CAD– status did not significantly impact 2-year mortality (hazard ratio [HR], 0.68; 95% confidence interval [95%CI], 0.21–2.21), while both CAG+CAD+ (HR, 1.90; 95%CI, 1.23–2.95), as well as CAG– status (HR, 1.81; 95%CI, 1.23–2.95) were associated with increased mortality.

Guidelines do not take a position for or against medical management in NSTEMI, but take a clear stand (class I indication) in favor of an invasive strategy as opposed to a conservative approach.² The choice of how to manage patients after coronary angiography is left to the discretion of the treating physicians. This approach follows the design of the invasive vs conservative management trials in NSTEMI, in which the investigators had the freedom to revascularize patients in the invasive arm or not (although revascularization was generally encouraged) and, in the case of revascularization, they were free to propose to the patient either percutaneous coronary intervention or coronary artery bypass surgery.^{3,4} The EPICOR study showed a high rate of invasive strategy, as 78.8% of the patients underwent coronary angiography (CAG+). This high prevalence of an invasive strategy was favored by the fact that 70% of the hospitals enrolling in EPICOR had an onsite cardiac catheterization laboratory (while the total number of patients enrolled in centers with a cardiac catheterization laboratory was not described). Therefore, this may not be representative of the reality of many countries included in the study. Accordingly, the presence of a cardiac catheterization facility onsite was identified in EPICOR as the main predictor for the performance of coronary angiography on multivariate analysis (odds ratio [OR], 46.76; 95%CI, 22.40–97.58). Major differences in terms of invasive strategy use were observed across the continents: taking Western Europe (North) as a reference, on multivariate analysis, the OR for patients to undergo coronary

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angiography were as low as 0.04 (95%CI, 0.02–0.11) in Latin America and 0.15 (95%CI, 0.06–0.35) in Eastern Europe.

Guidelines not only recommend an invasive strategy over a conservative approach in NSTEMI but equally give guidance in terms of maximum recommended delay between symptom onset and coronary angiography. While for most non-ST-segment elevation myocardial infarction patients the maximum recommended delay is 24 hours, patients with very high-risk criteria (ie, hemodynamic instability or cardiogenic shock, recurrent or ongoing chest pain refractory to medical treatment, life-threatening arrhythmias or cardiac arrest, mechanical complications of myocardial infarction, acute heart failure related to acute coronary syndrome or recurrent dynamic ST-T wave changes, especially ST-elevation) require a ST-segment elevation myocardial infarction-like management with coronary angiography within 2 hours.² Finally, for patients without troponin elevation, the time window for coronary angiography is 72 hours (if additional risk factors are present) or a conservative strategy (with or without a stress test) can be an alternative option. As timing between symptom onset and coronary angiography was not reported in EPICOR, this aspect of adherence to guidelines cannot be addressed.

According to the medications at discharge, evidence-based drug regimens were broadly offered in all patient categories, whether they were revascularized or not. If we exclude CAG+CAD- patients, in whom the administration of preventive regimen for coronary artery disease may be questionable, the proportion of patients receiving evidence-based drugs was high across the groups (coronary revascularization, CAG-, CAG+CAD+): > 90% for aspirin, > 70% P2Y₁₂ inhibitors, > 85% for statins, > 80% for betablockers, > 70% for angiotensin converting enzyme inhibitors. As patients were enrolled from 2010 to 2011, a time when prasugrel was entering the market while ticagrelor had not yet been approved in the majority of countries, it is understandable that the vast majority of patients received clopidogrel as the P2Y₁₂ inhibitor.

Was the increased mortality observed in CAG- and CAG+CAD+ patients in EPICOR related to an inappropriate withholding of coronary angiography and revascularization, respectively? Likely not, based on the favorable prevalence of the invasive strategy, as well as the high adherence to other evidence-based treatments. However, this question will remain with no final answer, as the reasons for not performing angiography in CAG- patients and for not carrying out coronary revascularization in CAG+CAD+ patients were not tracked in EPICOR.

An increased mortality in NSTEMI patients treated conservatively without coronary angiography has been reported on multiple occasions. In the French Registry of Acute ST-Elevation or Non-ST-Elevation Myocardial Infarction (FAST-MI), a conservative strategy as opposed to an invasive approach was identified as an independent predictor of short- and long-term mortality (at 30 days: HR, 3.19; 95%CI, 1.79–5.67; at 1-year: HR, 2.28; 95%CI, 1.60–3.26; at 5 years: HR, 1.63; 95%CI, 1.28–2.07).⁵ Similarly, an analysis of the Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes (TRILOGY ACS) trial showed that NSTEMI patients who did undergo coronary angiography had lower rates of the primary composite endpoint of cardiovascular death, myocardial infarction, or stroke at 30 months (12.8% vs 16.5%; HR, 0.63; 95%CI, 0.53–0.75) than patients who did not undergo coronary angiography.^{6,7} A subanalysis of Can Rapid Stratification of Unstable Angina Patients Suppress Adverse Outcomes (CRUSADE) well described the paradoxical use of coronary angiography in NSTEMI: patients with the greatest probability of having severe coronary artery disease were the least likely to undergo cardiac catheterization.^{8,9}

With respect to the group of patients who did undergo coronary angiography but were not revascularized (CAG+CAD-), 2 recent subgroup analyses of the Superior Yield of the New Strategy of

Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors [SYNERGY] trial and of the Early Glycoprotein IIb/IIIa Inhibition in Non-ST-Segment Elevation Acute Coronary Syndromes [EARLY ACS] trial reported that up to one-third of patients with significant coronary artery disease did not undergo revascularization. The reported reasons were an estimated low risk of recurrent coronary events or a high risk of periprocedural complications related to unfavorable coronary anatomy, severe left ventricular dysfunction, or comorbidities.^{10,11}

In this analysis of EPICOR, age > 75 years was independently associated with a lower probability of undergoing coronary angiography (OR, 0.38; 95%CI, 0.28–0.53; $P < .0001$). Similarly, patients aged > 75 years had a lower probability of undergoing revascularization following coronary angiography (OR, 0.73; 95%CI, 0.55–0.98; $P = .0348$). In an analysis of the Global Registry of Acute Coronary Events (GRACE) registry, NSTEMI patients older than 75 years underwent coronary angiography and revascularization less often than younger patients.¹² In the PLATO study, an invasive management was planned in a lower proportion of patients aged ≥ 75 years (61.5%) compared with younger patients (73.9%) ($P < .0001$).¹³ Age *per se* should not be a factor precluding access to coronary angiography and revascularization in NSTEMI. Accordingly, the randomized controlled After Eighty trial demonstrated the superiority of the invasive strategy over a conservative approach in 457 NSTEMI patients aged 80 years or more.¹⁴ At a median follow-up of 1.5 years, the primary composite outcome (myocardial infarction, need for urgent revascularization, stroke, and death) occurred in 40.6% in the invasive strategy group vs 61.4% in the conservative group (HR, 0.53; 95%CI, 0.41–0.69). In the elderly, the 2015 European Society of Cardiology NSTEMI guidelines—published before the release of the After Eighty trial—recommend an invasive strategy, if appropriate, after careful evaluation of comorbidities, life expectancy, quality of life, frailty, and patient preferences.²

In conclusion, the work of Bueno et al. should be praised for drawing the attention to the ill-defined group of NSTEMI patients not undergoing coronary revascularization, which includes patients not undergoing coronary angiography, those undergoing angiography demonstrating coronary artery disease but not undergoing revascularization, and patients with no significant coronary artery disease on angiography. With the exception of the latter group, patients treated medically had higher mortality than patients who benefited from revascularization. More investigations are needed to understand the reasons for not offering coronary angiography to NSTEMI patients and, among those with significant disease on angiography, for not providing revascularization.¹⁵ The After Eighty trial has clearly shown us that age *per se* should not be used as a reason to withhold an invasive strategy and, if appropriate, revascularization.

CONFLICTS OF INTEREST

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