

Treatment Strategies and Risk Stratification in Acute Coronary Syndrome: How Do We Identify Patients Who Would Benefit From Early Invasive Treatment?

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Patients presenting with acute or rapid onset of ischemic chest pain may be diagnosed on admission as having acute coronary syndrome (ACS). Despite the heterogeneous nature of the disease and the wide spectrum of signs and symptoms, ACS is a working diagnosis that implies a common pathophysiology: damage of the atherosclerotic vessel wall, usually in the form of rupture of a thin-cap-fibro-atheroma or vulnerable plaque, intimal dissection or endothelial denudation, with superimposed intracoronary thrombus formation resulting in a reduction in bloodflow to the myocardium. On the basis of the standard 12-lead electrocardiogram on admission, we generally distinguish between patients with ST-segment elevation myocardial infarction (STEMI) who have complete occlusion of an epicardial coronary artery requiring immediate reperfusion therapy, and patients with non-STEMI ACS (NSTEMACS) in whom the coronary artery is usually not completely occluded but there is reduction in blood flow, causing ischemia. In patients with STEMI, immediate reperfusion therapy, if possible with primary percutaneous coronary intervention in dedicated centers, is now the recommended approach. In patients with NSTEMACS, initial anti-ischemic and anti-thrombotic medical therapy may reduce intracoronary thrombus burden and improve coronary flow to such an extent that ischemia is completely alleviated. Medically stabilized patients may undergo ischemia detection with exercise testing at a later timepoint. However, for many years there has been fierce debate whether revascularization therapy or an early invasive—or aggressive—approach may be beneficial in patients with NSTEMACS. Large

registries have shown diverging results, although most studies have suggested that revascularization is associated with better clinical outcome.^{1,2}

Randomized studies conducted during the last decade have also shown divergent results, in part because of differences in the design of the studies and the patient populations randomized and partly due to the fact that clinical practice and revascularization techniques have changed substantially over the years. Meta-analyses of randomized studies have shown that an early invasive strategy does not reduce mortality but that there is a reduction in the endpoint of death or myocardial infarction, in particular in high risk patients.³

High risk features include a positive cardiac troponin, the presence of diabetes mellitus, hemodynamic or rhythmic instability, and ST-segment deviation on the electrocardiogram. Both American and European guidelines recommend an early invasive approach—angiography within 24-72 hours and subsequent revascularization—in patients with intermediate and high risk and a less aggressive approach in patients at low risk.^{4,5} In patients at low risk, the risk of an invasive approach might not outweigh the benefit, taking into account that the absolute risk reduction may be modest. Several subgroups such as female patients, the elderly and patients with moderate to severe renal dysfunction were underrepresented in the randomized studies. Although the guidelines recommend a careful assessment of risk versus benefit, in particular the risk of bleeding, which is associated with poor prognosis, the recommendation of an early invasive approach applies also to women, the elderly and patients with renal insufficiency.

In a recent study in which we combined the European strategy trials with long-term follow-up (the Framingham and Fast Revascularization During Instability in Coronary Artery Disease-II trial [FRISC-II], the Randomized Intervention Trial of Unstable Angina-3 [RITA-3] and the Invasive Versus Conservative Treatment in Unstable Coronary Syndromes trial [ICTUS]) using a pooled patient database, a reduction of death

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or myocardial infarction at 5 years follow up was shown in low-, intermediate- and high-risk patients.⁶ Again, absolute risk reduction was of course the highest in the intermediate and high risk patients, emphasizing that risk stratification is important. Of note, there were large differences in the intensity of revascularization between the three trials when comparing the routine invasive with the selective invasive group; revascularization in the selective invasive group of the ICTUS study was similar to the revascularization in the routine invasive group in RITA-3.

Assessment of left ventricular systolic function was not performed in these studies, and the study by Palau et al in this issue of *Revista Española de Cardiología* is therefore timely and adds important information.⁷ Intuitively, it seems straightforward to suggest that the greatest benefit of revascularization will occur in patients with impaired systolic function because these patients will be at higher risk and because in part systolic dysfunction may be caused by ischemia and thus may be reversed by revascularization. Palau et al identify 23.4% of patients with systolic dysfunction on echocardiography, defined as ejection fraction <50%, among a single center cohort of 972 consecutive patients with NSTEMI. Death or myocardial infarction at a median of 24 months was more frequent in patients with systolic dysfunction (49.8% vs 25.5%). After adjustment for prognostic risk factors including propensity score for an invasive approach, catheterization was associated with a greater risk reduction in patients with systolic dysfunction with a hazard ratio of 0.47 (95% CI, 0.30-0.75) compared to those without systolic dysfunction (HR=0.09; 95% CI, 0.63-1.29). The study has several limitations: the endpoint includes all-cause mortality and there is no information concerning cardiac mortality or death due to progression of heart failure and no information concerning left ventricular function at follow-up.

Thus, we are not informed about the mechanism by which the benefit is achieved. In addition, propensity score modelling cannot fully adjust for all confounding and therefore the study is hypothesis

generating. Importantly, the study emphasizes that the measurement of left ventricular function is paramount in the diagnostic work-up of patients with NSTEMI. One cannot but fully agree with the conclusions of the authors: future randomized studies are needed to confirm the present results.

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