Editorial

Prime time for the sweet spot in timing of coronary invasive approach in patients with non-ST elevation myocardial infarction

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Provenance: This is an invited Editorial commissioned by the Section Editor Hai-Long Dai (Department of Cardiology, Yan'an Affiliated Hospital of Kunming Medical University, Yunnan Province, China).

Comment on: Jobs A, Mehta SR, Montalescot G, *et al.* Optimal timing of an invasive strategy in patients with non-ST-elevation acute coronary syndrome: a meta-analysis of randomised trials. Lancet 2017;390:737-46.

Submitted Nov 08, 2017. Accepted for publication Nov 23, 2017.
doi: 10.21037/jtd.2017.11.125
View this article at: http://dx.doi.org/10.21037/jtd.2017.11.125

Acute coronary syndromes (ACS) continue to represent a major cause of morbidity and mortality worldwide. In the past decade data from the United States and Europe reported decreased incidence of ST-elevation myocardial infarction (STE-ACS) with an increase in non-ST-elevation myocardial infarction (NSTE-ACS) (1-3). As compared to STE-ACS patients, during initial admission, NSTE-ACS patients are at lower risk for death, but over time death rates become comparable with a trend towards increased mortality in the latter group (4). NSTE-ACS therefore constitutes a challenge in cardiology.

The superiority of an invasive strategy compared to a conservative strategy in NSTE-ACS is well established (5,6). However, there is an ongoing debate on the optimal timing of coronary angiography and percutaneous intervention (PCI) in NSTE-ACS patients. Theoretically, an early approach may allow rapid diagnosis, earlier mechanical revascularization, and shorter hospital stays; there may however be potential for an early hazard when intervening on unstable plaques with fresh thrombus. Conversely, a delayed strategy may yield benefits through plaque passivation by optimal medical treatment followed by intervention on more stabilized ("cooled") plaques; this potential advantage, however, may be counterbalanced by a higher risk for events while waiting for angiography. Currently there are ten randomized controlled trials (RCTs) that have compared early versus delayed intervention in NSTE-ACS patients with a large variation in timing, ranging from immediate up to 24 hours in the early group (7-17). Temporal differences of revascularization were even more pronounced in the delayed groups. In the Timing of Intervention in Acute Coronary Syndromes TIMACS trial, the primary combined end point (death, new MI, or stroke at 6 months) did not differ significantly between the early (within 24 hours of presentation) and delayed groups (any time >36 hours following presentation), although a significant decrease in the rate of death and MI was noted in the prespecified subgroup with high Global Registry of Acute Coronary Events (GRACE) risk scores (>140) having early intervention (14.1% *vs.* 21.6%). However, none of the studies was powered for mortality or single endpoint analysis. The first study to highlight this uncertainty in

timing and inconclusive evidence available is a recent meta-analysis (18). In this large-scale analysis there was no signal of benefit in mortality between early (less than 20 hours after hospitalization or randomization for RCTs) *vs.* delayed strategies neither in the randomized nor in the observational cohort. Similarly, no clear benefit in myocardial infarction rates or major bleeding complications (albeit with a trend towards numerical reduction in early group) was observed. Overall, the analysis suggests the safety, but not a clear benefit of early *vs.* delayed approach. Based on these results, the 2015 European Society of Cardiology (ESC) guidelines recommend PCI within up to 72 hours for patients not at high risk. The variable time frames evaluated in the individual studies, as well as the risk profile of the investigated populations, are reflected in the uncertainty and variations of classes and levels of recommendations of current guidelines across the Atlantic. On the other hand, they share transitioning of suggested timing from 48 hours to within 24 hours for distinct risk groups. These recommendations are mainly based on subgroup analysis of the TIMACS trial, which was not powered for sub-group survival analysis. Briefly, the most recent 2015 ESC NSTE-ACS guidelines recommend an immediate invasive strategy within 2 hours in patients at highest risk including those being hemodynamic unstable (class IC) (4). All other NSTE-ACS patients need to be stratified, mainly using GRACE score. High and intermediate risk patients should undergo PCI within 24 and 72 hours respectively (classes IA). The 2014 American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend early invasive strategy for management of patients with NSTE-ACS and refractory angina or electrical or hemodynamic insufficiency (class IB), initially stabilized patients with NSTE-ACS and high risk of clinical events (class IA) (19). The early invasive approach (within 12 to 24 hours of presentation) to reduce ischemic complications is also recommended in initially stabilized high-risk patients with NSTE-ACS (class IIA).

Recently, a meta-analysis of individual patient data by Jobs *et al.* found overall similar results with mortality rates being comparable in the early invasive versus delayed invasive as previously observed in the analysis by Navarese *et al.* (10,18). This new study adds information by including data on sub-groups of seven of the ten available RCTs on this topic for the first time. Jobs *et al.* show decreased all-cause mortality in four sub-groups of patients defined to be at high-risk undergoing an early invasive approach: Diabetic patients (HR, 0.67; 95% CI, 0.46–0.99), patients with elevated biomarkers (HR, 0.761; 95% CI, 0.581–0.996), patients older than 75 years (HR, 0.65; 95% CI, 0.45–0.99) and those evidencing GRACE scores higher than 140 (HR, 0.70; 95% CI, 0.52–0.95). Although confidence intervals were below 1.0 (identity point), test for interaction was non-significant in any of these sub-groups, limiting those findings to a descriptive and hypothesis-generating nature. However, these trends are in accordance to data from a large number of patients in pooled findings from four observational studies in which patients are deemed at higher risk and less selected than those coming from randomized studies, as shown by Navarese *et al.*: in 77,499 patients (without data on risk sub-groups) early intervention was associated with a non-significant decrease in mortality (18).

Taking together these elements there is no clear evidence for superiority—at least in terms of major hard endpoints—of either approach (early or delayed) in the overall NSTE-ACS population. To provide a definitive answer, a large randomized trial including a total of 20,900 patients to have 90% statistical power to detect the mortality decrease in the NSTE-ACS patients would be required. This study is probably unfeasible due to costs constraints and the limited interest from an industry perspective.

However, lumping together available data, it seems reasonable to predict a benefit in subgroups at higher risk—judged by clinical or score criteria—who need to be treated more aggressively. The crucial question is the precise characterization of patients at higher risk. Biomarkers might be of certain value in identifying these subjects, however concerns arise on the objective value of "positive cardiac enzymes" defined in the article with a binary criterion. This point assumes particular relevance nowadays given the widespeared adoption in routine of precise diagnostic tests as hs-TNT which are reported as continuous values. Most of the studies investigated in this meta-analysis have indeed been conducted in the pre-hs-TnT area with LDH and creatinine kinase cut-offs used as reference tool. However, the value of both parameters in ACS was recently questioned (20). Continuous effort to develop new tools for risk stratification is warranted as known risk factors might be of limited use under certain circumstances. For instance, it is well known that diabetic patients are at high risk for an adverse cardiac event, but it might be difficult to diagnose or exclude diabetes in the acute setting and stratify patients accordingly. Combining a troponin cut-off with novel (cardiac or non-cardiac) biomarkers could possibly improve risk stratification of NSTE-ACS patients (21,22). Certainly, older patients who are known to reap higher benefits from

invasive treatment in general, are considered a high-risk category, but one would certainly like to identify patients at high risk not solely based on age (23).

High GRACE score constitutes a further subgroup in the analysis by Jobs: GRACE has considerably improved the definition of risk in ACS setting, providing higher accuracy and discrimination for risk stratification than other scores as TIMI and PURSUIT. This score—which includes information on both age and cardiac enzymes—therefore seems to be the best risk stratification tool available. However, delving deeper into the included items several limitations emerge. First of all, GRACE score was developed more than a decade ago; therefore, different variables have gained or lost importance as prognostic indicators. Although the Killip classification finds some use today—mainly as a component of other risk scores—it has lost much of its value because heart failure is no longer such an overwhelming threat to most patients with ACS. Long-term outcomes such as revascularization rates may nowadays major role given the declined rates of mortality of ACS patients. These apparently softer endpoints can actually be driven by higher refractory ischemia rates as the composite endpoint of revascularizations/refractory ischemia was found to be significantly reduced with an early strategy in the meta-analysis by Navarese *et al.* This should be factored in in future risk stratifications.

Since age makes an exponential contribution to the GRACE score, on an individual patient basis, risk of younger patients with a flow-limiting culprit coronary artery lesion may be underestimated. Moreover, GRACE includes elevated cardiac enzymes classified as a binary criterion not accounting for the various ranges of cardiac enzymes at presentation. Therefore, older studies in NSTE-ACS in the meta-analysis by Jobs *et al.* not including hs-TnT, but using previous markers, need to be interpreted with caution. Development of novel stratification tools in contemporary practice is therefore a warranted step.

Further, nearly all patients included in RCTs investigated by Jobs *et al.* were initially hemodynamically stable. Patient instability plays certainly great role in rushing the patient to the cath lab as soon as possible—a concept that is already in the guidelines. Therefore, in unstable patients there is no reason to delay invasive procedure.

From an economic standpoint, as shown in the previous paper by Navarese *et al.*, length of hospital stay is significantly lower in patients undergoing an early intervention strategy, which might be of interest socio-economically due to more efficient health-care resource usage. This is a point to be considered in future economic evaluations to treat patients more cost-efficiently.

In summary, there is not enough evidence in favor of early versus delayed strategy in the general NSTE-ACS population with comparable mortality rates, as shown first by the analysis by Navarese *et al.* and reaffirmed in the most recent individual patient data meta-analysis. As we are entering individualized medicine era, there is the unmet need to fine-tune diagnoses and risk stratification with novel biomarkers and more contemporary clinical parameters to achieve the sweet spot in timing of revascularization of NSTE-ACS patients.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Navarese EP, Wernly B, Lichtenauer M, Pepe M, Wanha W, Ferrante G, Frediani L, Veulemans V, Zeus T, Westenfeld R, Jung C, Gurbel PA. Prime time for the sweet spot in timing of coronary invasive approach in patients with non-ST elevation myocardial infarction. J Thorac Dis 2018;10(1):17-20. doi: 10.21037/jtd.2017.11.125

