Risk stratification following non-ST segment elevation myocardial infarction: Is the glass half-full or half-empty?

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In the current issue of *The Canadian Journal of Cardiology*, Zia et al (pages 1073-1079) reported their interesting findings from two registries of acute coronary syndrome (ACS) patients – the United States (US) Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) National Quality Improvement Initiative (n=88,097, 465 hospitals) and the Canadian ACS Registries I and II (n=1270, 51 hospitals, and n=1473, 36 hospitals, respectively). The authors observed a higher rate of invasive procedures in the US than in Canada, as have other researchers. However, the authors' main goal was not a direct comparison of care between countries, but rather an assessment of how each country uses its invasive cardiac resources as a function of risk stratification. Entry criteria into both registries were not identical, but the authors have assembled similar high-risk populations by concentrating on non-ST segment elevation myocardial infarction (NSTEMI) populations or unstable angina (UA) patients with accompanying electrocardiographic changes. Risk was stratified according to the previously validated Platelet glycoprotein IIb-IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) risk model.

The authors report a paradoxically declining use of invasive procedures in the higher-risk patients, and remarkably, this observation is independent of the baseline use and availability of invasive cardiac procedures. Specifically in the US, low-risk patients had a 76.2% use of coronary angiography during their hospitalization, which decreased to 53.2% in the high-risk group – a 23% absolute reduction. The Canadian registry had a 63.5% angiographic intervention rate in the lowest-risk and 40.5% in the high-risk groups, for an identical 23% absolute reduction. The authors concluded that “increased use of guidelines recommendations in patients with high-risk NSTEMI ACS is expected to have a significant impact on ACS mortality rates in both the US and Canada”.

The present editorial briefly examines whether further increases in invasive procedures for high-risk patients are indeed likely to lead to further increased health benefits. The American College of Cardiology and the American Heart Association 2002 guidelines on UA/NSTEMI (1), which state that high-risk patients should be treated with an aggressive invasive approach (class 1 recommendation), certainly support this viewpoint. No clinician would doubt the value of an invasive approach in patients with refractory angina or those with hemodynamic or electrical instability. However, an August 2007 update of these guidelines (2) also stated that “in initially stabilized UA/NSTEMI patients, an initial conservative (selective invasive) strategy may be considered as a treatment option. The decision to implement an initial conservative (versus initial invasive) strategy in these patients may be made by considering physician and patient preference. The Writing Committee also believes that additional comparative trials of the selective invasive with the routine initial invasive

strategies are indicated...troponin alone might no longer be an adequate criterion for strategy selection, especially with increasingly sensitive troponin assays. The degree of troponin elevation and other high-risk clinical factors taken together should be considered in selecting a treatment strategy”. It is intellectually refreshing to see that the current guidelines have re-evaluated increased troponin levels as a unique arbitrator of clinical management strategies and now place this as one, albeit an important one, predictor in the overall risk evaluation of the patient.

Thus, the most recent guidelines (2) are less categorical in recommending that a routine invasive approach brings better outcomes in some patients previously considered to be at high risk. What might have caused this slight shift of opinion? Perhaps the recent re-emergence of medical therapy as an equivalent treatment to revascularizations as seen in stable angina (3) and following STEMI (4) has influenced this equilibrium. The recent results of the Invasive versus Conservative Treatment in Unstable coronary Syndromes (ICTUS) trial (5) of 1200 high-risk ACS patients (troponin-positive with either electrocardiographic changes or a prior history of coronary artery disease) randomly assigned to an early invasive strategy or to a more conservative (selectively invasive) strategy have also undoubtedly contributed substantially to this re-evaluation. In this trial, patients received optimal medical therapy, and the primary end point of death, nonfatal MI or rehospitalization for anginal symptoms within one year after random assignment was not different between the two groups (RR 1.07, 95% CI 0.87 to 1.33; P=0.33). MI was also more frequent in the early invasive group management (15.0% versus 10.0%; P=0.005). After three years, MI remained more frequent in the early invasive strategy group (106 [18.3%] versus 69 [12.3%]; hazard ratio 1.61, 95% CI 1.19 to 2.18; P=0.002) (6).

Perhaps clinicians are also now more aware of the hazards in extrapolating results from idealized clinical trials to the real world, especially when substantial differences exist in the different populations. The new guidelines (2) explicitly recognize these nuances, and an early invasive strategy has been recommended for patients who have an elevated risk for clinical events, provided that they are without serious comorbidities or contraindications to such procedures. In this regard, it is pertinent to examine the entrance criteria for the two main randomized controlled trials (FRagmin and fast revascularisation during InStability in Coronary artery disease [FRISC II] [7] and Treat Angina with aggrastat and determine Cost of therapy with an Invasive or Conservative Strategy [TACTICS] [8]) supporting a general invasive approach and compare them with the patient populations from the registries used in the study by Zia et al. In FRISC II, no patients were older than 75 years, while the average age of the high-risk group in the Zia et al study was 76 to 77 years. Both FRISC II and TACTICS excluded all patients with renal failure, but 11% to 18% of patients in the two registries had this condition. Consequently, clinicians might have rightly

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been very wary in assuming an automatic translation of any potential randomized controlled trial invasive strategy benefits occurring in the unselected patients from these registries.

Clinicians might also have critically assessed the primary data on which the recommendations for a generalized invasive policy were predicated and determined that the evidence is less than compelling. The recommendation for a routine invasive approach in UA/NSTEMI patients is largely based on seven randomized controlled trials, the results of which have been combined in a meta-analysis (9) showing a reduction in the combined end point of death or MI in the selective invasive group to the routine invasive group after a mean 17-month follow-up (OR 0.82, 95% CI 0.72 to 0.93; $P=0.001$). However, the routine invasive strategy was not associated with improved long-term mortality (6.0% versus 5.5%; OR 0.92, 95% CI 0.77 to 1.09; $P=0.33$), and actually exhibited higher in-hospital mortality (1.1% versus 1.8% for selective versus routine, respectively [OR 1.60, 95% CI 1.14 to 2.25; $P=0.007$]) and an increased composite end point of death or MI (3.8% versus 5.2%; OR 1.36, 95% CI 1.12 to 1.66; $P=0.002$).

Moreover, recent comparative trials of invasive versus conservative strategies appear to have been biased against the conservative selective approach. For example, the invasive arms have generally received a dual antiplatelet drug compared with a single agent in the conservative arms, and this alone may account for some of the improved clinical outcomes (10). Also, recent trials have used more stringent criteria to diagnose MI in the invasive arm, possibly resulting in an ascertainment bias. The most extreme example is the Value of first day angiography/angioplasty in evolving Non-ST segment elevation myocardial infarction (VINO) (11) study, in which the protocol prohibited counting any MIs in the routine invasive arm for 72 h following the intervention. FRISC II

restricted angiographic crossovers in the selective group to patients with at least 3 mm of ST depression, a ridiculously high bar that it is not reflective of most clinical practice, and in essence making the comparison one of a routine invasive strategy against an inappropriately conservative approach. Thus, the protocols of the most recent studies might have been biased against the selective invasive approach and, consequently, overestimated the benefits of a routine invasive strategy.

The success of conservative approach in the ICTUS (5) trial might have been due not only to improved optimal medical therapy but also to the large number of patients receiving revascularization (40%). In general, it appears that there is little difference in outcomes in randomized controlled trials between an invasive strategy with an approximate 70% revascularization rate and selective strategy once a 30% to 40% revascularization crossover rate has been attained in the conservative group. Indeed, the largest benefit in favour of a systematic routine invasive approach was in the FRISC II trial (7), in which revascularizations in the conservative group were inappropriately limited to only 9%.

The totality of the evidence therefore suggests that a selective invasive policy that cumulates in a revascularization rate of approximately 40% following an admission for UA/NSTEMI is likely to provide equal health benefits to a more systematic invasive approach. In the paper by Zia et al, it appears that the high-risk groups in both Canada and the US are near the optimal invasive rate catheterization rate. Recall also that there is no evidence for improved outcomes with a routine invasive strategy in low-risk patients. Therefore, it appears that the paradox observed by Zia et al represents not the underuse of resources among the high-risk patients in the NSTEMI group, but rather the marked overuse of invasive cardiac resources in low-risk patients.

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