Treatment strategies and risk stratification in non ST elevation acute coronary syndromes

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ACS describes the spectrum of clinical manifestations which follow disruption of a coronary arterial plaque, complicated by thrombosis, embolization and varying degrees of obstruction to myocardial perfusion. The clinical features depend upon extent and severity of myocardial ischemia. In the clinical setting the term ‘acute coronary syndrome’ is used as an initial working diagnosis. The 12-lead electrocardiogram (ECG) segregates patients into those presenting with ST-segment elevation (approximately one third), and those presenting without ST-segment elevation (approximately two third). Patients with ST-segment elevation are likely to have acute, total occlusion of a coronary artery which will eventually lead to extensive myocardial ischemia and transmural myocardial infarction. These patients should be considered for immediate percutaneous coronary intervention in order to open the occluded coronary artery and restore perfusion. In patients without ST-segment elevation (nSTE-ACS), severe myocardial ischemia will result in subendocardial myocardial infarction which can be detected by measuring concentration of markers of myocardial injury such as troponin T and CK-MB in a blood sample. The release of these sensitive markers of myocardial necrosis is regarded as indicative of myocardial cell necrosis and fulfills the definition of non ST-elevation myocardial infarction (NSTEMI). If no rise in markers is detected, the term unstable angina is used and non-cardiac differential diagnoses must be considered.

The therapeutic management is guided by the final diagnosis and risk assessment. The management of nSTE-ACS and NSTEMI patients includes four therapeutic tools: antiplatelet agents (e.g. aspirin, clopidogrel), anticoagulants (e.g. heparin), anti-ischemic agents (e.g. beta-blockers) and coronary revascularization.

The ICTUS trial

In the ICTUS trial 1200 patients with nSTE-ACS and an elevated cardiac troponin were enrolled from 42 hospitals in the Netherlands. Patients were randomly assigned either to an early invasive strategy, including early routine catheterisation and revascularisation where appropriate, or to a more selective invasive strategy, where catheterisation was done if the patient had refractory angina or documented ischemia on a pre-discharge exercise test. Patients received aspirin daily, enoxaparin for 48 hours, and abciximab at the time of percutaneous coronary intervention. The use of clopidogrel and intensive lipid-lowering therapy starting at the time of randomization was recommended. The primary end point was a composite of death, nonfatal myocardial infarction (procedure-related and spontaneous MI), or rehospitalization for anginal symptoms within one year after randomization.
The main results of the ICTUS trial

The main result of the ICTUS study ([chapter 2]) showed that we could not demonstrate that an early invasive strategy was superior to a selectively invasive strategy in nSTE-ACS patients with an elevated cardiac troponin T level. The cumulative rate of the primary end-point was 22.7% in the early invasive group and 21.2% in the selective invasive group (relative risk, 1.07; 95% confidence interval, 0.87 to 1.33; P=0.33). Mortality was the same in the two groups (2.5%). Myocardial infarction was significantly more frequent in the group assigned to early invasive management (15.0 % vs. 10.0 %, P=0.005). The higher incidence of myocardial infarction in the early invasive group was driven in large part by relatively small infarctions related to percutaneous coronary intervention. Rehospitalization for anginal symptoms was less frequent in the early invasive group (7.4 % vs. 10.9 %, P=0.04).

Long-term follow-up of the ICTUS trial ([chapter 3 and 4]) confirmed our findings at one year and did not show that an early invasive strategy is better than a more selective invasive strategy. The estimated 3-year cumulative event rate for the composite end-point death, myocardial infarction, or rehospitalisation for anginal symptoms was similar in the two treatment groups (30.0% in the early invasive vs. 26.0% in the selective invasive group; p=0.09). At 4-year follow-up no difference in death from all causes or cardiovascular death was seen between the two strategies. The 3-year event rate of myocardial infarction was higher in the early invasive group than in the selective invasive group. This difference was entirely due to the occurrence of more procedural related myocardial infarctions in the early invasive strategy group. The cumulative event rate for spontaneous myocardial infarction was similar, with 7.4% in the early invasive group and 7.2% in the selective invasive group (p=0.94).

Long-term follow up is only available from the FRISC-II, RITA-3 and ICTUS study. When long-term results from these three trials are combined, there is only a non-significant trend towards fewer deaths with an (early) invasive strategy in patients with nSTE-ACS. In contrast, post-hoc analyses from several large observational studies have demonstrated that revascularization in hospital is associated with a substantial reduction in mortality compared with medical treatment. In [chapter 5], we performed a retrospective analysis with the data from the ICTUS trial as if the data had been obtained by means of an observational study. Similar to retrospective analyses from observational studies, actual revascularization during hospital admission was associated with lower mortality and fewer MIs in ICTUS, even after the use of appropriate risk adjustment techniques. This apparent discrepancy is primarily driven by the poor prognosis in...
patients who underwent angiography but were not revascularized because of co-morbidities and anticipated high procedure-related risks. Thus, patients with non-STE-ACS that are not revascularized form a heterogeneous group of patients that either have no significant coronary artery disease or have very extensive or diffuse coronary artery disease or significant co-morbidities that make revascularization unattractive. Therefore, whether an early invasive strategy leads to a better outcome than a selective invasive strategy cannot be inferred from the retrospective observation that revascularized patients have a better prognosis in non-randomized studies.

There are several possible explanations for the observed apparent differences in outcome between the present study and previous trials. One reason that could explain our results is the high percentage of patients that were revascularized in the selective invasive group compared with the other trials. In the FRISC-II study, the revascularization rate during initial hospitalization was 13% in the non-invasive group and 76% in the invasive treatment group; in the RITA 3 10% and 44%; and in the ICTUS study 40% and 76%. Thus, the revascularization rate in the invasive treatment group of the RITA 3 study is nearly identical to the revascularization rate in the non-invasive treatment group in the ICTUS study (44% versus 40%). Instead of comparing an invasive strategy to a non-invasive strategy, the ICTUS trial compared routine, early revascularization to less aggressive, delayed intervention.

Our results and those from the FRISC-II and RITA 3 trials differ in the incidence of myocardial infarctions in both treatment strategies. The rate for spontaneous myocardial infarction was lower in the selective invasive group of the ICTUS trial compared to the non-invasive group of the FRISC-II trial. The low rate of spontaneous myocardial infarctions in ICTUS could be due to the compliance to early and long-term medical treatment in our study. Patients in the ICTUS trial were treated with aspirin, enoxaparin, intensive lipid-lowering therapy and glycoprotein IIb/IIIa inhibitors at the time of PCI. In the early invasive treatment strategy we observed a high incidence of myocardial infarction, particularly during hospitalization, confirming previous findings of the FRISC II researchers that there is an early hazard associated with early revascularization. As in FRISC II, most myocardial infarctions in the early-invasive-strategy group in our study were relatively small procedure-related myocardial infarctions that were detected with carefully timed and frequent measurements of CK-MB levels.
In chapters 6 - 9 we described our analyses into whether additional risk stratification can identify patients that may benefit most from an early invasive treatment strategy.

In chapter 6, we showed that the standard 12-lead admission ECG remains as an easy, readily available, inexpensive method of risk stratifying patients with nSTE-ACS. Cumulative ST-segment deviation of at least 1 mm on the admission ECG identifies patients at risk for subsequent adverse cardiac events. We showed that patients with cumulative ST-segment deviation of at least 1 mm, more frequently fail medical therapy and are at increased risk of spontaneous MI after discharge when no coronary angiography was performed during initial hospitalization.

In Chapter 7 we showed that NT-proBNP is a strong independent predictor of mortality by 1 year, but we found no association between NT-proBNP and recurrent MI. Sudden death and progression of congestive heart failure were important causes of death in the highest quartile of NT-proBNP. However, we could not demonstrate a benefit of an early invasive strategy in patients who have nSTE-ACS with both an elevated NT-proBNP and cTnT.

Cystatin C (a novel marker for kidney function) was shown to be a potential marker to improve risk stratification in our study population (Chapter 8). Patients were stratified according to tertiles of cystatin C concentration at baseline. Mild to moderate renal dysfunction (third tertile) was associated with a higher risk of death or spontaneous MI during long-term follow-up. We compared the effect of an early invasive strategy to a selective invasive strategy in each tertile of cystatin C for descriptive purpose. In patients with mild to moderate renal dysfunction (third tertile), a non-significant trend was seen in favor of the selective invasive strategy. We observed a lower event rate in the middle tertile for an early invasive strategy, but given the relatively small sample size, these results should be regarded with caution. Our findings and the findings of other trials suggest that there might be an altered risk versus benefit ratio in nSTE-ACS patients with impaired renal function undergoing invasive procedures.

Despite an overall benefit for patients randomized to an invasive strategy in the FRISC II and the RITA 3 trials, subgroup analyses from these studies showed that an invasive strategy may be associated with a higher risk of death or MI in women. For this reason, we conducted a collaborative meta-analysis to examine the benefits and risks of an invasive strategy in women vs. in men with nSTE-ACS. In chapter 9, we showed that an
invasive strategy has a comparable benefit in men and high-risk women for reducing the composite end-point of death, MI, or rehospitalization with ACS. In contrast, an invasive strategy does not appear to substantially benefit women in the absence of biomarker elevation and moreover may potentially increase the risk of death or MI. Our data provide evidence to support the updated American College of Cardiology—American Heart Association guidelines that now recommend that a conservative strategy should be used in low-risk women with NSTE ACS.

**Impact of our findings**

After publication of the results of the ICTUS trial the guidelines of the American College of Cardiology–American Heart Association but not the European Society of Cardiology have been changed. In the most recent ACC/AHA guidelines it is now stated: In initially stabilized patients, an initially conservative (i.e., a selective invasive) strategy may be considered as a treatment strategy for nSTE-ACS patients (without serious comorbidities or contraindications to such procedures) who have an elevated risk for clinical events, including those who are troponin positive. The decision to implement an initial conservative (vs. initial invasive) strategy in these patients may consider physician and patient preference (Class IIb, Level of Evidence: C).

**Recommendations for clinical practice**

Since the publication of the ICTUS trial results, physicians may feel more confident that an early invasive strategy and a selectively invasive strategy are equivalent and accepted treatment options in nSTE-ACS patients with an elevated troponin T. For clinical decision-making and subsequent patient management, risk stratification of nSTE-ACS patients is essential. An early invasive strategy is indicated in nSTE-ACS patients who have refractory angina or hemodynamic or electrical instability. An early invasive and a selective invasive treatment strategy are equivalent treatment strategies in nSTE-ACS patients with an elevated troponin T, even if these patients have high levels of NT-proBNP at admission or if they have mild to moderate renal dysfunction. In these patients, the treatment strategy chosen in daily clinical practice can depend on physician preference, patient preference and co-morbidity. More recently, two randomized trials (TIMACS and ABOARD) addressed the question of timing of invasive procedures. These trials compared a strategy of immediate intervention compared with a strategy of intervention deferred to the next working day. These trials showed that early intervention did not differ greatly from delayed intervention in preventing major cardiac events.
Regardless of the treatment strategy ultimately selected, the medical therapy for nSTE-ACS patients should include the early use of aspirin, a thienopyridine, an anticoagulant, beta blockade, statin therapy, intravenous nitroglycerin (in the early phase), and probably an angiotensin-converting enzyme (ACE) inhibitor. Platelet-glycoprotein IIb/IIIa inhibitors may not be required during initial medical management.

The results of the ICTUS trial suggest that patients with nSTE-ACS with an elevated troponine T who stabilize on medical therapy can safely wait for an invasive procedure. But the question remains: is it worth the wait? In other words, do patients who wait for angiography have equally good outcomes and levels of satisfaction as those managed with upfront angiography? Until further research is completed, a dualistic approach will dominate the management of nSTE-ACS.

**Directions for future research**

In the new era of comparative effectiveness research, costs and quality metrics should be measured alongside hard clinical outcomes to ultimately define how various strategies reduce resource utilization and achieve optimal benefits for patients with NSTEMI.

All the major strategy trials excluded patients older than 75-80 years of age and patients with moderate to severe impaired renal function. With changing demographics, it is important to investigate whether an early invasive strategy in nSTE-ACS patients older than 80 years of age reduces the Incidents of death or morbidity compared to a selective invasive strategy. In the decades to come, these patients will rapidly grow in numbers.

Also, little is known about the effect of an early invasive strategy among patients with renal impairment since these patients are most often excluded. Future research should investigate whether there is an altered risk versus benefit ratio in nSTE-ACS patients with impaired renal function undergoing invasive procedures.