

# Invasive Management of Non-ST Elevation Acute Coronary Syndromes: Lessons From RITA-3 and Other Randomised Trials

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Over the last decade there has been intense research interest in the management of non-ST segment elevation acute coronary syndromes (NSTACS). Much of this research has focussed on optimization of initial pharmacological intervention and the role of anti-platelet agents, anti-thrombins, and lipid-lowering treatment in NSTACS is now established.<sup>1-5</sup>

Nevertheless, following initial medical stabilization patients with NSTACS remain at increased risk of death or myocardial infarction and subsequent treatment is controversial.<sup>6,7</sup> Some cardiologists advocate early coronary arteriography and myocardial revascularisation in all suitable patients, in the belief that mechanical intervention will improve clinical outcome. Proponents of the «invasive» strategy argue that early coronary arteriography allows timely risk stratification and identification of high risk patients who will benefit from myocardial revascularisation. Other clinicians recommend a more conservative approach with intensive medical treatment to stabilize the acute ischaemic syndrome, and coronary arteriography only for patients with refractory symptoms or provokable ischaemia on non-invasive testing. Advocates of the conservative strategy cite growing evidence that acute coronary syndromes may be associated with a systemic inflammatory process and atherosclerotic plaque disruption in more than one coronary vascular territory.<sup>8,9</sup> These observations undermine the rationale for focal percutaneous coronary intervention in a single «culprit» vessel, judged to be the cause of the episode of acute myocardial ischaemia.

Uncertainties about the best management strategy for patients with NSTACS are evident in registry studies, which have shown considerable geographical

variation in the use of invasive procedures.<sup>10,11</sup> Moreover, in the OASIS registry high rates of invasive cardiac procedures were associated with low rates of refractory angina and readmission to hospital, but did not appear to influence the risk of cardiovascular death or myocardial infarction.<sup>11</sup>

## RANDOMISED TRIALS

To resolve the controversy about the management of NSTACS several large randomized clinical trials have compared the effects of early invasive and conservative treatment strategies.<sup>12-18</sup> These trials now include the third Randomised Intervention Treatment of Unstable Angina trial (RITA-3), which recently published results in *The Lancet*.<sup>19</sup>

Two early trials showed no advantage of an invasive strategy but have limited relevance to contemporary practice because they were conducted before the widespread use of coronary stents and modern anti-thrombotic therapy.<sup>12,13</sup> Moreover the crossover rates in these trials were relatively high and at one year the revascularisation rates in the invasive and conservative groups differed by only 6% (TIMI-3b)<sup>12</sup> and 11% (VANQWISH).<sup>13</sup> Interpretation of the results of VANQWISH is further complicated by a high surgical mortality rate, and an excess of cardiac events amongst patients assigned to invasive treatment who were managed conservatively.<sup>13</sup>

The TACTICS-TIMI 18 trial randomized 2220 patients with non-ST elevation acute coronary syndromes to invasive or conservative treatment strategies. All patients were treated with aspirin, heparin, and tirofiban. At 6 months 61% of the invasive group and 44% of the conservative group had undergone revascularisation. The primary endpoint of death, myocardial infarction, or re-admission to hospital with acute coronary syndrome within 6 months occurred in 15.9% of the invasive group and 19.4% of the conservative group ( $P=0.025$ ). This difference was partly due to a higher readmission rate in the conservative group, but the rates of death and

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myocardial infarction were also lower in the invasive arm (7.3% vs 9.5% at 6 months;  $P<.05$ ).<sup>14</sup> These benefits of intervention appeared to be confined to patients with elevated baseline serum levels of troponin.<sup>20</sup>

FRISC-2 is the largest trial to compare invasive and conservative treatment strategies in patients with NSTACS, with 2457 randomized patients.<sup>15,21</sup> All patients were treated with aspirin and anti-thrombin (unfractionated heparin or dalteparin in a factorial trial design) but only a small proportion of patients were given a glycoprotein IIb-IIIa receptor antagonist. In FRISC-2 there was wide separation of the treatment strategies and after 1 year 78% of the invasive group and 43% of the conservative group had undergone a revascularisation procedure. The invasive strategy was associated with a higher risk of death or myocardial infarction in the first two weeks after randomisation, but thereafter the rates of both components of the composite endpoint were consistently lower than in the conservative group. After 2 years the early invasive strategy was associated with a reduction in mortality (3.7% vs 5.4%;  $P=.038$ ), myocardial infarction (9.2% vs 12.7%;  $P=.005$ ) and the combined endpoint (12.1% vs 16.3%;  $P=.003$ ).<sup>22</sup> These benefits were greatest amongst patients with elevated serum levels of troponin and ST-segment depression on the baseline electrocardiogram.<sup>23,24</sup> Recently the FRISC-2 investigators have also reported that an elevated plasma level of interleukin-6, a systemic marker of inflammation, predicted outcome and identified patients who benefit most from a strategy of early invasive management.<sup>25</sup> The invasive strategy was also associated with improved symptoms and lower hospital re-admission rates.

### RITA-3

RITA-3 is the most recent trial of early invasive versus conservative treatment in NSTACS to report results. RITA-3 was designed to test the hypothesis that routine early coronary arteriography, with myocardial revascularisation when clinically indicated, is better than a conservative medical strategy in patients with unstable angina and non-ST elevation myocardial infarction.

Patients presenting with chest pain of presumed cardiac origin and electrocardiographic, prior arteriographic, or serum cardiac marker evidence of myocardial ischaemia were eligible for randomization. From November 1997 to October 2001 the trial enrolled 1810 patients from 45 hospitals in England and Scotland. The majority (92%) had electrocardiographic evidence of myocardial ischaemia at baseline and 41% had ST segment deviation of at least 0.1 mV.

All randomized patients were treated with anti-ischaemic medication, aspirin, and enoxaparin (1 mg/kg twice daily for 2-8 days), but IIb-IIIa receptor antagonists were used at the discretion of the supervising clinician. Of 895 patients assigned to the invasive arm 815 (97%) underwent coronary arteriography a median of 2 days after randomisation, and significant coronary artery disease was found in 78%. Percutaneous coronary intervention was done in 311 patients, with an angiographic success rate of 96%. Stents were inserted in 88% of these patients, 96% of whom were discharged on a thienopyridine. Coronary artery bypass surgery was done in 184 patients with a 30-day mortality of 3.0%. Overall a revascularisation procedure was done during the index hospital admission in 45% of patients assigned to the invasive strategy. By contrast 16% of patients assigned to the conservative strategy underwent coronary arteriography and 10% underwent a revascularisation procedure during the index hospital admission. After one year revascularisation rates had increased to 57% in the invasive arm and 28% in the conservative arm.

The co-primary trial endpoints were the combined rate of death, myocardial infarction or refractory angina at four months, and the combined rate of death or myocardial infarction at one year. Refractory angina was defined as recurrence of cardiac chest pain with electrocardiographic evidence of myocardial ischaemia, and provoking myocardial revascularisation within 24 hours. After discharge from hospital refractory angina was diagnosed if the patient was readmitted with an episode of cardiac chest pain associated with new electrocardiographic evidence of myocardial ischaemia. At four months the incidence of the primary endpoint of death, myocardial infarction or refractory angina was 9.6% in the intervention arm and 14.5% in the conservative arm (risk ratio, 0.72; 95% CI, 0.58-0.90;  $P=.003$ ). This difference was mainly due to a reduction in refractory angina, and was maintained at one year.

The co-primary endpoint of death or non-fatal myocardial infarction at one year occurred in 7.0% of the intervention group and 8.3% of the conservative group, but this difference did not quite reach statistical significance ( $P=.058$ ). This trend was maintained throughout all known follow-up, and after a median two years 10.6% in the intervention arm and 12.9% in the conservative arm had died or had a myocardial infarct (hazard ratio, 0.83; 95% CI, 0.63-1.08).

### TRIAL COMPARISONS

These large randomised trials have demonstrated consistent beneficial effects of an invasive strategy in patients with NSTACS. Nevertheless, comparisons of the trials are complicated by differences in patient risk

TABLE 1. The three largest trials of invasive versus conservative treatment policies in NSTACS

	FRISC-2		TACTICS-TIMI 18		RITA-3	
Trial characteristics						
Number of patients	2457		2220		1810	
Recruitment	1996-1998		1997-1999		1997-2001	
Median age, years	66		62		62	
Female, %	30		34		38	
Diabetes mellitus, %	12		28		13	
Previous MI, %	22		39		28	
ST segment deviation, %	45		38		41	
	Invasive	Conservative	Invasive	Conservative	Invasive	Conservative
Coronary arteriography						
In-hospital or <7days, %	96	10	97	51	96	16
Within 6-12 months, %	99	47	98	61	97	48
Coronary artery disease						
0, %	14	13	22	-		
1-2 vessels, %	56	44	55	-		
3 vessels and LMS, %	31	43	22	-		
Revascularisation						
PCI within 6-12 months, %	44	21	42	29	36	16
Stent use in PCI patients, %	62	69	83		88	90
GP IIb-IIIa antagonist use in PCI patients, %	10	10	94	59	24	
Thienopyridine after PCI, %	?	?	?	?	96	82
CABG within 6-12 months, %	38	23	22	16	22	12
Revascularisation within 6-12 months, %	78	43	61	44	57	28
Outcome within 6-12 months						
Death or MI	10.4	14.1	7.3	9.5	7.6	8.3
Death, MI, severe angina leading to readmission/revascularisation, %	42.2	13.2	15.9	19.4	13.5	18.4

MI indicates myocardial infarction; LMS, left main stem; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft.

profile, anti-thrombotic medication, and interventional therapy (Table 1). For instance patients in RITA-3 were more likely to be female and have normal coronary arteries. In FRISC-2 fewer patients were treated with stents and only 10% of the patients undergoing percutaneous coronary intervention were treated with a glycoprotein IIb-IIIa receptor antagonist. More liberal use of these agents might have reduced the risks of percutaneous intervention and increased the overall benefit of an invasive strategy in both FRISC-2 and RITA-3.

In all of the trials early coronary arteriography in the invasive arm identified some patients with normal coronary arteries or only mild coronary artery disease, for whom myocardial revascularisation is unlikely to confer benefit. Furthermore, in several of the trials the effects of myocardial revascularisation may have been diluted by early crossover to the invasive strategy from the conservative group. It is therefore possible that the trials substantially underestimate the benefit of myocardial revascularisation in patients with NSTACS.

Comparison of the results of these trials is also confounded by different definitions of myocardial

infarction. In RITA-3 a consistent definition of myocardial infarction was used in both arms of the trial. By contrast in FRISC-2 and TACTICS-TIMI 18 a three-fold rise in a biochemical marker of myocardial necrosis was required to diagnose myocardial infarction in patients undergoing a percutaneous coronary intervention procedure, but in patients managed conservatively the definition was less stringent. In both of these trials myocardial infarction amongst patients undergoing coronary artery bypass surgery was diagnosed only when new Q waves appeared on the electrocardiogram, although it is known that elevation of cardiac enzymes following coronary artery bypass surgery occurs frequently and has an adverse effect on outcome.<sup>26</sup> Patients undergoing revascularisation procedures, most of whom were in the invasive arms of these trials, were therefore subjected to a less sensitive definition of myocardial infarction. This difference in definition of myocardial infarction between the invasive and conservative arms of the FRISC-2 and TACTICS-TIMI 18 trials may have contributed to the reported differences in the rates of myocardial infarction.

In total 8 randomised clinical trials have compared invasive and conservative treatment strategies in patients with NSTACS, including three small trials with fewer than 200 patients.<sup>16-18</sup> Combined analysis of all these trials shows a risk ratio for the combined endpoint of death and myocardial infarction of 0.88 (95% CI, 0.78-0.99), indicating a small benefit from the interventional strategy<sup>19</sup> (Figure 1). These data suggest that the small procedural risks associated with invasive management of NSTACS may be counterbalanced by a subsequent reduction in the risk of non-procedural events. Nevertheless, the data require cautious interpretation as there is significant statistical heterogeneity between the trials, and overall the combined data do not provide conclusive evidence of benefit.

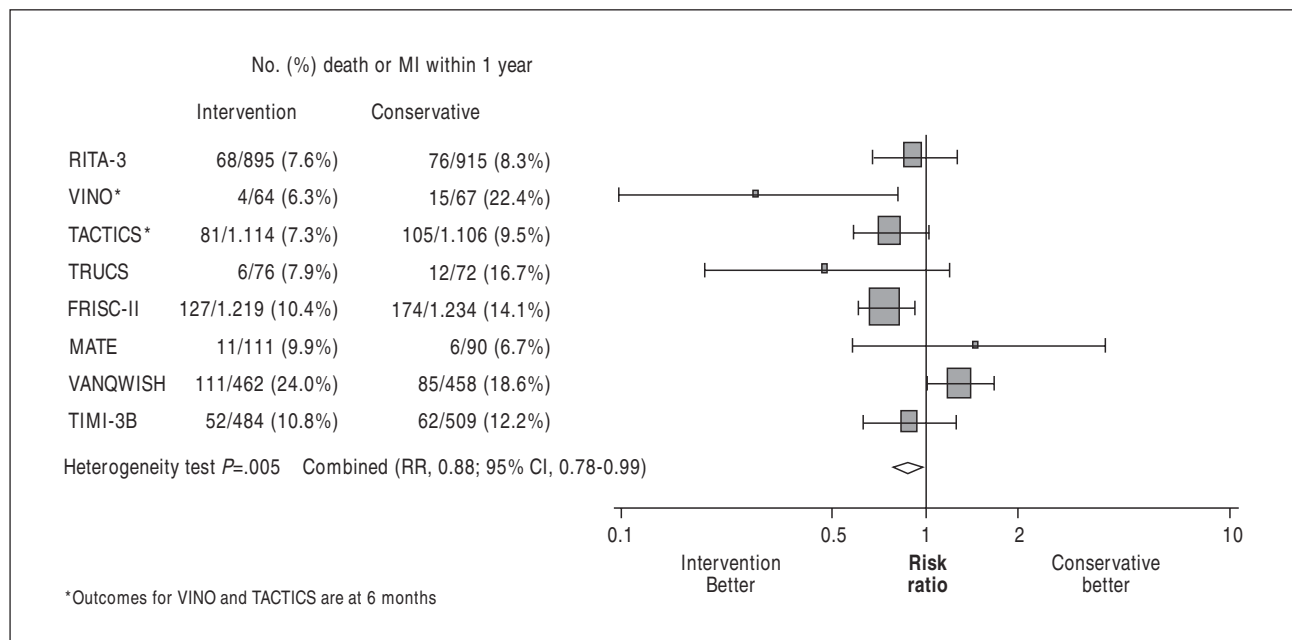
## INFLUENCE OF GENDER

There is uncertainty about the influence of gender on the outcome and response to treatment of acute coronary syndromes. Women presenting with acute coronary syndromes are typically older than their male counterparts, but are less likely to have previous myocardial infarction, elevations of serum cardiac markers, or significant coronary artery disease. On the other hand women may be at higher risk of complications during myocardial revascularisation procedures, and women treated with fibrinolysis for ST-elevation acute coronary syndromes have

consistently been reported to be at increased risk of death or reinfarction.

Some registry studies suggest that women may have better outcomes than men after non-ST elevation acute coronary syndromes but evidence from the major randomised trials of invasive versus conservative management strategies is conflicting.<sup>27,28</sup> In TACTICS-TIMI 18 the benefits of the invasive strategy were seen equally in men and women with no evidence of an interaction between gender and treatment effect.<sup>26</sup> By contrast, in FRISC-2 the one year rates of death or myocardial infarction in female patients were 12.4% and 10.5% in the invasive and conservative groups respectively, but amongst men these event rates were 9.6% and 15.8% respectively.<sup>29</sup>

In RITA-3 subgroup analyses also revealed an interaction with gender. At four months the rates of death, myocardial infarction or refractory angina amongst male patients were 8.8% and 17.3% in the invasive and conservative groups respectively, but amongst female patients the rates were 10.9% and 9.6%. Similarly, at one year the rate of death or nonfatal infarction was lower amongst male patients in the invasive group (7.0% vs 10.1%), but amongst female patients the invasive strategy was associated with increased risk (8.6% vs 5.1%; interaction  $P=.011$ ).<sup>19</sup> Thus the effects of an invasive strategy in female patients with NSTACS remain uncertain, and further research is required before definitive treatment recommendations for women can be made.



**Fig. 1.** Reported incidence of myocardial infarction and/or death in eight trials of intervention versus conservative management for non-ST elevation acute coronary syndromes. Reprinted with permission from Elsevier.<sup>19</sup>



## ECONOMIC COSTS

The benefits of an early invasive strategy in patients with NSTACS must be balanced against the additional economic costs of routine coronary coronariography and myocardial revascularisation. An economic analysis of the FRISC-2 trial demonstrated that an early invasive strategy incurred an additional cost of around 2700 euros when compared with the conservative strategy. The authors of this study calculated incremental cost-effectiveness ratios for the invasive strategy of around 160 000 euros per avoided death, and 72 000 euros per avoided death or myocardial infarction, during the first year of follow-up.<sup>30</sup> These cost-effectiveness ratios fall outside the range which many European countries consider economically acceptable, but are likely to become more favourable if the benefits of the invasive strategy are maintained in the long term.

In TACTICS-TIMI 18 the average total cost of invasive treatment was only \$586 higher than the cost of the conservative treatment at 6 months, and cost-effectiveness ratios based on projected life expectancy were estimated at around \$13 000 per year of life gained.<sup>31</sup> The more favourable cost-effectiveness ratio in TACTICS-TIMI 18 requires cautious interpretation because of the high crossover rate and hence increased costs amongst patients in the conservative arm.

Thus the economic arguments in favour of a routine early invasive strategy are not compelling, but the planned economic analysis of the RITA-3 trial will provide further information about the relative cost and cost-effectiveness of the 2 treatment strategies.

## CONCLUSIONS

Overall the trials of early invasive versus conservative management in patients with NSTACS provide convincing evidence of a beneficial effect of invasive treatment on refractory angina and recurrent ischaemia. The effects of an invasive strategy on mortality and risk of myocardial infarction are less certain, and the prognostic advantage seen in FRISC-2 has not been confirmed in all trials or by meta-analysis. The role of the invasive strategy in women also remains uncertain. Nevertheless, the available evidence suggests that high risk patients, including those with ST segment depression or elevated serum cardiac markers, do benefit from early coronary arteriography. Recent guidelines emphasize the importance of risk stratification to identify patients who will benefit from invasive investigation, and suggest that low risk patients can be managed safely with an initial conservative policy.<sup>32</sup>

A number of questions remain unresolved. For instance the optimal timing of coronary arteriography

in patients with NSTACS has not been determined. In FRISC-2 and RITA-3 patients were initially stabilised with intensive medical therapy, and optimal anti-thrombotic and anti-ischaemic medication may be as important as revascularisation. Recent studies suggest that clopidogrel has a role in the treatment of patients with NSTACS, particularly after coronary stent implantation, but whether combination therapy with a thienopyridine and glycoprotein IIb/IIIa receptor antagonist confers additive benefit is unknown.

The relative effects of surgical and percutaneous coronary intervention on outcome are also uncertain and the best revascularisation strategy for many different patient subgroups has not been determined. Patients with NSTACS are often treated by intervention on a single «culprit» artery judged to be the cause of the acute ischaemic syndrome, but the long term implications of partial revascularisation also require further evaluation. Finally the impact of drug coated stents and other emerging technologies in patients with NSTACS is unknown. All of these questions can only be answered by further research, aimed at optimising the management of this challenging and important group of patients.

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