Treatment strategies and risk stratification in acute coronary syndromes
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EFFECTS OF AGE ON LONG-TERM OUTCOMES AFTER A ROUTINE INVASIVE OR SELECTIVE INVASIVE STRATEGY IN PATIENTS PRESENTING WITH NON-ST SEGMENT ELEVATION ACUTE CORONARY SYNDROMES: A COLLABORATIVE ANALYSIS OF INDIVIDUAL DATA FROM THE FRISC II - ICTUS - RITA-3 (FIR) TRIALS


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ABSTRACT

Objective: To perform a patient-pooled analysis of a routine invasive (RI) versus selective invasive (SI) strategy in elderly patients with non-ST-segment elevation acute coronary syndrome.

Methods: Meta-analysis of patient-pooled data of the FRISC II–ICTUS–RITA-3 (FIR) studies. (Un)adjusted hazard ratios (HR) were calculated with Cox regression, with adjustments for variables associated with age and outcomes. The main outcome was 5-year cardiovascular death or myocardial infarction (MI).

Results: Regarding the 5-year composite of cardiovascular death or MI, the RI strategy was associated with a lower hazard in the 65-74 years (Hazard Ratio [HR] 0.72, 95%CI:0.58-0.90) and the ≥75 years (HR 0.71, 95%CI:0.55-0.91), but not in the <65 years category (HR 1.11, 95%CI:0.90-1.38), P=0.001 for interaction between treatment strategy and age. The interaction was driven by an excess of early MIs in patients <65 years of age while there was no heterogeneity between age groups concerning cardiovascular death. The benefits were smaller for women than men (P for interaction 0.009). After adjustment for other clinical risk factors the HRs remained similar.

Conclusion: The current analysis of the FIR dataset shows that the long-term benefit of the RI over the SI strategy is attenuated in younger patients <65 years of age and in females by the raised risk of early events which seem to have no consequences for long-term cardiovascular mortality. No other clinical risk factors were able to identify patients with differential responses to a RI strategy.
INTRODUCTION

The most recent guidelines for myocardial revascularisation recommend a routine invasive over a selective invasive approach in patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) at high-risk for recurrent events. Although higher age has been identified as a non-modifiable risk factor in the most recent strategy trials, recommendations regarding treatment strategies are generally hampered by lower patient numbers with increasing age. This is especially true in patients aged 75 years or older, an underexposed subgroup that is often excluded from major trials. There is limited randomized data available, and previous studies comparing these strategies in the elderly patients were performed before the availability of stents and glycoprotein IIb/IIIa inhibitors, so few data are available regarding more contemporary practice. In addition the underrepresentation in clinical trials, registry data show that elderly patients with NSTE-ACS are less likely to undergo cardiac catheterisation and revascularisation, partly explained by an underestimation of risk by the physician.

Besides the higher risk for recurrent events with older age, elderly patients are an important subgroup because of the heterogeneity in cognitive and physical functioning and more comorbidities, which may alter the course after ACS. Moreover, elderly patients will constitute an important subgroup of patients, keeping in mind the gradually increasing age in the Western World.

In the current analysis of the FRISC II – ICTUS – RITA-3 (FIR) patient-pooled dataset, we evaluated long-term outcomes in a subgroup of elderly patients randomized to a routine invasive versus a selective invasive strategy. Moreover, we are able to compare these outcomes across other clinical categories of baseline risk.

METHODS

Setting and data collection

The principal investigators (LW, RJdW, KAF) initiated the FIR collaborative analysis, and a protocol was written which included the main prespecified analyses and a core set of variables. Investigators from the three trials provided individual patient data to form the FIR patient-pooled database, including variables on demographics, clinical history, risk factors for coronary artery disease, baseline electrocardiographic characteristics, laboratory results and 5-year clinical outcomes. Datasets from each trial were sent for merging to the coordinating Academic Medical Center in Amsterdam, the Netherlands. The merged database was checked for completeness and consistency by all three participating sites.

Study population and procedures

The details of the design of the FRISC II, ICTUS, and RITA-3 trials have been described previously. The three trials compared a routine invasive strategy with a selective invasive strategy in NSTE-ACS patients. Patients in the routine invasive
group were scheduled to undergo early coronary angiography (within 24-48 hours in ICTUS, within 72 hours in RITA-3), with subsequent revascularisation when appropriate. In the FRISC II trial, the aim was to perform angiography and revascularisation, if appropriate, within seven days. Coronary artery bypass grafting (CABG) was recommended with severe left main stem or three-vessel disease. The selective invasive strategy consisted of initial medical treatment with coronary angiography and revascularisation only in the case of refractory angina despite optimal medical treatment (or in the case of hemodynamic or rhythmic instability in ICTUS). In the FRISC II and ICTUS trials, a pre-discharge ischemia detection test was performed.

Age
Based on recommendations of the American Heart Association on Clinical Cardiology and the Society of Geriatric Cardiology, we formed the following three age study groups for our analysis: patients aged <65 years, patients aged 65 to 74 years, and patients aged ≥75. Regarding the original trials, patients were eligible for FRISC II if age was ≤75 years (or older unless revascularisation was deemed inappropriate) and for ICTUS if age was between 18 and 80. No age-related exclusion criteria were defined in RITA-3.

Outcomes
The main outcomes for the current analysis were the 5-year composite outcome cardiovascular (CV) death or MI and the individual components CV death and MI. CV death was defined as death from any cause, unless an unequivocal noncardiovascular cause could be established. The original definition of MI per trial was used because it was not possible to readjudicate individual events to accommodate a common definition. In the FRISC II trial, MI was defined by the occurrence of two of the following conventional criteria; typical chest pain, diagnostic electrocardiographic recording (new Q waves), and elevation in one cardiac biomarker above the upper limit of normal (ULN) with spontaneous MIs, or elevation in one cardiac biomarker up to 1.5 the ULN with procedure-related MIs. In the RITA-3 trial, MI was defined as diagnostic electrocardiographic recording (new Q waves) or by the combination of a typical clinical event, electrocardiographic evidence of acute infarction and an elevation in one cardiac biomarker up to twice the ULN. In ICTUS, MI was defined as myocardial necrosis in the setting of myocardial ischemia. Myocardial necrosis was defined as an elevation in one cardiac biomarker above the ULN with spontaneous MIs, or three times the ULN in case of a procedure-related MI. We used both spontaneous and procedure-related MIs from all three studies in our current analysis.

Data concerning in-hospital major bleeding was available from the ICTUS and RITA-3 trials. Major bleeding was defined in ICTUS as fatal bleeding, intracranial bleeding, a need for blood transfusion, a decrease of 3 mmol per liter or more in hemoglobin levels, and bleeding resulting in hemodynamic compromise. Major bleeding in RITA-3 was defined as bleeding requiring surgical intervention or transfusion.
Statistical analysis
Cumulative event rates for unadjusted analyses were estimated by the Kaplan-Meier method and compared with the log-rank test. Follow-up for the composite outcome was censored at the actual date of last contact or at five years, whichever came first. We investigated the relation between treatment strategy and outcomes in the three age study groups in three sets of Cox proportional-hazards models: unadjusted models, multivariable models with adjustment for the FIR risk score and study, and multivariable models with adjustment for variables significantly related to age and outcomes. The FIR risk score indicates 5-year risk for cardiovascular death or MI and is based on the following variables: age, BMI, diabetes, hypertension, previous MI, and the presence of ST-depression ≥0.1mV. Interaction between age as a continuous variable and treatment strategy was assessed by including an interaction term in the Cox proportional-hazards models. In prespecified analyses we analyzed the relation between treatment strategy and outcomes in the three age study groups according to gender or baseline risk as indicated by the FIR risk score. Because we specifically wanted to examine the impact of age, the most important contributor to the FIR score, age was excluded from the risk score model, and we redefined the low-risk, intermediate-risk and high-risk category cut-offs in patients assuming they received the selective invasive strategy that resulted in roughly one-third of outcomes per group. The proportional hazards assumption for all analyses was verified graphically, no relevant violations were observed.

RESULTS
A total of 5467 NSTE-ACS patients were included in the FIR dataset, of whom 2807 patients (51.3%) were younger than 65 years, 1821 patients (33.3%) were between 65 and 74 years and 839 patients (15.3%) were 75 years or older. The baseline characteristics are presented in Table 1.

Generally, with increasing age, there were fewer men, an increased history of MI or revascularisation, and a higher baseline risk profile as indicated by the FIR risk score (even after excluding age as one of the risk score components). Regarding risk factors for coronary artery disease, the older patients were less often smokers and had less hypercholesterolemia, while diabetes mellitus and hypertension were more common.

Revascularisation over time
At 5-year follow-up, 74.1% of all patients underwent revascularisation by percutaneous coronary intervention or CABG in the routine invasive group, while 49.6% underwent revascularisation in the selective invasive group. These revascularization rates were respectively 80% versus 53% in FRISC II, 81% versus 60% in ICTUS, and 62% versus 39% in RITA-3. Figure 1 shows the cumulative revascularisation over time according to treatment strategy and age study group. No difference in revascularisation was observed between the three age groups in the routine invasive (P=0.33) or the selective invasive strategy (P=0.13). No heterogeneity was observed across studies.
With increasing age, revascularisation was more often performed with CABG (30.5% in the <65 years, 46.6% in the 65-74 years and 53.5%) in the ≥75 years category (P-value for trend <0.001). Regarding PCI or both procedures on the same day, these percentages were respectively 68.9%, 52.8%, 46.5% and 0.5%, 0.6% and 0.0%.

### Five-year outcomes

In the total population, the cumulative event rates for the composite outcome CV death or MI, and its individual components were respectively 17.1% (907/5467), 7.4% (399/5467) and 12.3% (644/5467). For each of these outcomes, increasing 5-year event rates were observed across the <65 years, 65-74 years and ≥75 years category.
categories (overall log-rank P<0.001 for all outcomes). The cumulative event rates are shown in Table 2.

Regarding treatment strategies, 15.9% of patients randomized to the routine invasive strategy experienced the composite outcome versus 18.3% in the selective invasive strategy (HR: 0.86, 95% CI: 0.76-0.98, P=0.03). The hazard ratios for the individual outcomes MI and cardiovascular mortality were respectively (HR: 0.83, 95% CI: 0.71-0.97, P=0.03) and (HR: 0.83 (95% CI: 0.68-1.01, P=0.07).

**Age**

When comparing a routine invasive strategy with a selective invasive strategy with regards to 5-year composite of CV death or MI, the routine invasive strategy was associated with a lower hazard in the 65-74 years category (unadjusted HR 0.72, 95% CI: 0.58-0.90, P=0.003) and the ≥75 years category (unadjusted HR 0.71, 95% CI: 0.55-0.91, P=0.007), but not in the <65 years category (HR 1.11, 95% CI: 0.90-1.38, P=0.33), P=0.001 for interaction between treatment strategy and age. This interaction was driven by a reduction of MIs in the 65-74 years category (unadjusted HR 0.69, 95% CI: 0.53-0.90, P=0.006) and the ≥75 years category (unadjusted HR 0.60, 95% CI: 0.43-0.83, P=0.002), while there was a numerical
excess of MI in the <65 years category (10.2% in the routine invasive versus 9.1% in the selective invasive group). Regarding CV death, no heterogeneity differences were observed. The Kaplan-Meier curves (Figure 2) indicated that the hazard in the <65 years age group was caused by early MIs. After adjustment for the FIR risk score and study or predictors for outcomes in multivariable Cox proportional-hazards models, the HRs did not materially alter. Cumulative event rates according to treatment strategy, unadjusted and adjusted HRs are presented in Table 3.

**Gender**

There was an interaction between treatment strategy and gender with a larger benefit in men than women (P for interaction 0.009). In male patients, the routine invasive strategy was associated with a lower hazard in the 65-74 years category (unadjusted HR 0.60, 95% CI: 0.47-0.79, P<0.001) and the ≥75 years category (unadjusted HR 0.63, 95% CI: 0.46-0.86, P=0.004), but not in the <65 years category (HR 1.04, 95% CI: 0.81-1.33, P=0.78), P for interaction <0.001. The interaction was mainly driven by the individual component MI while there was no heterogeneity regarding mortality. No difference between the treatment strategies was observed in any of the age categories in female patients regarding the composite or individual outcomes. The HRs for the composite outcome were (HR 1.34, 95% CI: 0.88-2.06, P=0.17) for <65 years, (HR 1.10, 95% CI: 0.74-1.62, P=0.66) for 65-74 years and (HR 0.87, 95% CI: 0.57-1.33, P=0.52) for ≥75 years, P for interaction 0.83. Figure 3 shows Kaplan-Meier curves for CV death or MI after a routine or selective invasive strategy according to age and gender indicating a larger early hazard and less long-term benefit in women than men regardless of age. After taking age and gender into account, other clinical risk factors did not interact with and were unable to further identify specific responses to a routine invasive strategy.

**Baseline risk profile**

We compared the treatment strategies regarding CV death or MI according to FIR baseline risk (without age as a component) in the different age categories. The FIR

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**Table 2: Cumulative event rates for composite and individual outcomes of death or myocardial infarction at 5-year follow-up.**

<table>
<thead>
<tr>
<th>Five-year outcome</th>
<th>&lt;65 years (n=2807)</th>
<th>65-74 years (n=1821)</th>
<th>≥75 years (n=839)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death or MI</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>CV death</td>
<td>328 (12.0%)</td>
<td>335 (18.9%)</td>
<td>244 (30.3%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MI</td>
<td>94 (3.4%)</td>
<td>156 (8.7%)</td>
<td>149 (18.5%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*P-value by log-rank test for overall comparisons
CV : cardiovascular, MI : myocardial infarction
MI included all spontaneous and procedure-related MIs.
Table 3. Cumulative event rates for 5-year composite and individual outcomes according to treatment strategy and age.

<table>
<thead>
<tr>
<th>Five-year outcome</th>
<th>Routine invasive</th>
<th>Selective invasive</th>
<th>Unadjusted HR (95% CI)</th>
<th>P-value</th>
<th>Adjusted HR (95% CI)</th>
<th>P-value</th>
<th>Adjusted HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death or MI</td>
<td>n/N (%)</td>
<td>420/2721 (15.9%)</td>
<td>487/2746 (18.3%)</td>
<td>0.86 (0.76-0.98)</td>
<td>0.03</td>
<td>0.81 (0.71-0.93)</td>
<td>0.002</td>
<td>0.81 (0.71-0.93)</td>
</tr>
<tr>
<td></td>
<td>Age Interaction</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>169/1383 (12.5%)</td>
<td>159/1424 (11.5%)</td>
<td>1.11 (0.90-1.38)</td>
<td>0.33</td>
<td>1.09 (0.87-1.35)</td>
<td>0.001</td>
<td>1.09 (0.87-1.35)</td>
<td>0.001</td>
</tr>
<tr>
<td>65-74 years</td>
<td>142/901 (16.1%)</td>
<td>193/920 (21.7%)</td>
<td>0.72 (0.58-0.90)</td>
<td>0.003</td>
<td>0.71 (0.57-0.88)</td>
<td>0.001</td>
<td>0.71 (0.57-0.89)</td>
<td>0.001</td>
</tr>
<tr>
<td>≥75 years</td>
<td>109/437 (26.1%)</td>
<td>135/402 (34.9%)</td>
<td>0.71 (0.55-0.91)</td>
<td>0.007</td>
<td>0.65 (0.50-0.84)</td>
<td>0.001</td>
<td>0.63 (0.49-0.82)</td>
<td>0.001</td>
</tr>
<tr>
<td>CV death</td>
<td>Total cohort</td>
<td>181/2721 (6.8%)</td>
<td>218/2746 (8.1%)</td>
<td>0.83 (0.68-1.01)</td>
<td>0.07</td>
<td>0.78 (0.64-0.96)</td>
<td>0.02</td>
<td>0.78 (0.64-0.96)</td>
</tr>
<tr>
<td></td>
<td>Age Interaction</td>
<td>0.89</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>42/1383 (3.1%)</td>
<td>52/1424 (3.7%)</td>
<td>0.84 (0.56-1.25)</td>
<td>0.39</td>
<td>0.84 (0.55-1.27)</td>
<td>0.87</td>
<td>0.85 (0.56-1.29)</td>
<td>0.87</td>
</tr>
<tr>
<td>65-74 years</td>
<td>68/901 (7.6%)</td>
<td>88/920 (9.8%)</td>
<td>0.78 (0.57-1.07)</td>
<td>0.12</td>
<td>0.76 (0.55-1.05)</td>
<td>0.92</td>
<td>0.76 (0.55-1.06)</td>
<td>0.92</td>
</tr>
<tr>
<td>≥75 years</td>
<td>71/437 (16.9%)</td>
<td>78/402 (20.2%)</td>
<td>0.80 (0.58-1.11)</td>
<td>0.18</td>
<td>0.77 (0.56-1.07)</td>
<td>0.01</td>
<td>0.77 (0.55-1.07)</td>
<td>0.01</td>
</tr>
<tr>
<td>MI</td>
<td>Total cohort</td>
<td>292/2721 (11.1%)</td>
<td>352/2746 (13.4%)</td>
<td>0.83 (0.71-0.97)</td>
<td>0.03</td>
<td>0.79 (0.68-0.93)</td>
<td>0.004</td>
<td>0.79 (0.68-0.93)</td>
</tr>
<tr>
<td></td>
<td>Age Interaction</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>137/1383 (10.2%)</td>
<td>126/1424 (9.1%)</td>
<td>1.14 (0.90-1.45)</td>
<td>0.29</td>
<td>1.10 (0.86-1.41)</td>
<td>1.10</td>
<td>1.10 (0.86-1.41)</td>
<td>1.10</td>
</tr>
<tr>
<td>65-74 years</td>
<td>93/901 (10.7%)</td>
<td>134/920 (15.3%)</td>
<td>0.69 (0.53-0.90)</td>
<td>0.006</td>
<td>0.70 (0.54-0.91)</td>
<td>0.51</td>
<td>0.70 (0.53-0.91)</td>
<td>0.51</td>
</tr>
<tr>
<td>≥75 years</td>
<td>62/437 (15.2%)</td>
<td>92/402 (24.7%)</td>
<td>0.60 (0.43-0.83)</td>
<td>0.002</td>
<td>0.52 (0.37-0.73)</td>
<td>0.51</td>
<td>0.52 (0.37-0.73)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

P-value from Cox regression model, interaction P-values are for interaction between treatment and age as a continuous variable.

*With adjustments for the FIR risk score and study.

With adjustments for body-mass index, gender, history of myocardial infarction/percutaneous coronary intervention/coronary artery bypass grafting, current smoking, hypertension, hypercholesterolemia, diabetes, ST-segment depression and study.

Abbreviations as in Table 2.
Figure 2. Kaplan-Meier curves for CV death or MI after a routine or selective invasive strategy according to age. P-value by the log-rank test.
low-risk group was redefined as a risk score of 0-2, the intermediate-risk as score 3-5, the high-risk group as score ≥6. In the three age study groups, no interaction was observed between treatment strategy and FIR baseline risk (P-value for interaction 0.41 in the age <65 years group, 0.56 in the 65-74 years group and 0.07 in the ≥75 years group). Figure 4 shows the distribution of patients in the redefined FIR risk groups according to age.

Bleeding
Of 3006 patients with available data regarding initial in-hospital bleeding, bleeding rates were significantly higher in older patients, 1.7% (29 bleeds) in the <65 years, 2.2% (21 bleeds) in the 65-74 years and 6.1% (23 bleeds) in the ≥75 years category (P<0.001 for trend). In total there were 44 (2.9%) in-hospital bleeds in the routine
invasive group compared to 29 (1.9%) in the selective invasive group (p=0.069). The number of bleeds was higher with the routine invasive strategy within each of the three age categories although numbers were small and P-values all above 0.1.

**DISCUSSION**

The current meta-analysis of the FRISC II – ICTUS and RITA-3 trials demonstrated that the long-term reduction in the composite of CV death or MI of the routine invasive strategy versus a selective invasive strategy is mainly seen in patients aged 65 or older. In younger patients <65 years of age this effect is attenuated by an excess of early MI. However, these events did not have consequences for effects on survival which showed no heterogeneity in relation to age. The early hazards were larger and the long-term benefits smaller in female patients in all age groups. Other clinical risk factors at baseline were not able to better identify specific responses to a routine invasive treatment strategy.

**Previous treatment strategy trials**

The TIMI IIIB and VANQWISH trials were performed in the early 1990s, before routine availability of coronary stents and glycoprotein IIb/IIIa inhibitors, and compared an early invasive with an early conservative strategy. Regarding outcomes in elderly patients, these trials yielded conflicting results. While the overall TIMI IIIB trial showed equivalence between treatment strategies, a reduction in 1-year death or MI was observed in elderly patients (≥65 years). In contrast, the VANQWISH trial suggested a potential hazard of early invasive treatment in patients aged above 60 years. This was partly explained because of a high 30-day event rate in high-risk patients undergoing CABG.

In one of the more contemporary studies, the TACTICS-TIMI 18, patients were randomized to an early invasive or conservative treatment strategy. At 6-month follow-up, a reduction in death or MI was observed with the early invasive strategy among patients 65 years of age or older. Outcomes were similar in patients younger than 65 years. Although the benefit was also observed in patients above 75 years of age, this was accompanied by significantly increased major bleeding. This was likely the result of the combination of the invasive procedure and the use of glycoprotein IIb/IIIa inhibitors. Glycoprotein IIb/IIIa inhibitors were used in 94% of the PCIs during initial hospitalisation in ICTUS. In RITA-3, glycoprotein inhibitors were used in around 25% of the PCI procedures. Our current results are in line with the TACTICS-TIMI 18 trial, and extend the evidence with sustained benefit at long-term follow-up. Although inhospital major bleeding was numerically higher with the routine invasive strategy compared with the selective invasive strategy, the number of bleeds was small and the evidence for a difference weak.

The long-term results of the FRISC II and RITA-3 trials, showed a benefit of a routine invasive strategy over a selective invasive strategy. This reduction in death and MI increased with increasing baseline-risk. While the assessment of baseline risk was based on multiple clinical factors collected at baseline, age
was one of the strongest contributors to baseline risk. Also, in the ICTUS trial, increasing event rates were observed with higher baseline-risk profiles, but no difference between treatment strategies was observed in any of the risk strata. This heterogeneity between the three pooled trials has also attenuated the reduction on both mortality and MI as observed in the FRISC II and RITA-3 trials, with less cross-over to revascularisation.

**Gender**

Taking gender into account, the benefit of the routine invasive strategy was mainly observed in men, as reported in previous meta-analyses. One of these analyses showed a benefit of the routine invasive strategy in female high-risk patients. In our current analysis, female patients aged 75 years or older were low in frequency, so results in this higher risk group should be interpreted with caution. The observed gender difference was mainly driven by the FRISC II and RITA-3 trials, which have previously shown that a reduction in death and MI was mainly observed in male patients. No clear gender differences were observed in ICTUS.

**Baseline risk profile**

A previous report on NSTE-ACS registry data discusses the risk-treatment paradox, showing that older higher risk patients are managed more conservatively. One possible explanation is the underestimation of the risk profile of elderly patients by physicians. The authors showed that the baseline risk profile, as indicated by the GRACE risk score was significantly higher in older patients. This is corroborated by our current results, showing higher FIR risk scores in older patients. Thus, the reason of under treatment of the elderly might be an overestimation of the procedural risk and an underestimation of the long-term benefits in elderly patients with more comorbidities indicating higher risk. However, the present results highlight that the additional clinical risk factors, beyond age and eventually gender, have no significant impact on the long-term benefits of a routine invasive treatment strategy. Accordingly these risk factors don’t seem useful but rather might be misleading if used for selection of patients for a routine invasive strategy. Although laboratory parameters might assist in this process, these were not completely available in the FIR-database. Finally, we have to keep in mind that there is a preferential recruitment of lower-risk patients into clinical trials, with a possibility that the very elderly patients were not recruited for the FIR trials.

**FIR risk score and treatment strategy**

We have previously shown that the FIR integer risk score, which reflects the baseline risk profile, can be used to identify patients who have the largest benefit of the routine invasive strategy. The current results show that the main driver of the FIR baseline risk profile is age, and that no other FIR risk score factors identify responders to the routine invasive strategy. Gender, which is no component of the FIR risk score, did assist in the identification of responders. In conclusion, although the FIR risk score adequately discriminates patients at low, intermediate or high risk for long-term
Outcomes, age and gender are the most important factors in the triage of patients to a routine or a selective invasive strategy in the FIR dataset. As mentioned above, laboratory parameters might assist in the selection of treatment strategies.

**Limitations**

Several limitations of the current analysis are worthy of note. First, there was heterogeneity between trials regarding the revascularisation rates and timing of revascularisation in the routine invasive and selective invasive strategies. The high revascularisation rate in the selective invasive arm in ICTUS will have attenuated the benefits of a routine invasive strategy. Second, the outcome MI was composed of all spontaneous and procedure-related MIs from the FRISC II, ICTUS and RITA-3 trials, and a uniform definition could not be achieved. The use of a uniform definition of MI would have allowed a more accurate assessment of treatment effects on the clinical outcomes spontaneous and procedure-related MI.

**CONCLUSION**

The current analysis of the FIR patient-pooled dataset indicates that the long-term benefit of the routine invasive strategy over the selective invasive strategy is attenuated in younger patients below 65 years and in women because of the raised risk of early events. However, these events seem to have no consequences...
for mortality. No other clinical risk factors were able to identify patients with differential responses to a routine invasive strategy.

ACKNOWLEDGEMENTS

We would like to thank all investigators from the FRISC II, ICTUS, and RITA-3 trials. Most importantly, we would like to thank all patients participating in these trials.

REFERENCE LIST


