TIMING OF ANGIOGRAPHY WITH A ROUTINE INVASIVE STRATEGY AND LONG-TERM OUTCOMES IN NON-ST-ELEVATION ACUTE CORONARY SYNDROME. A COLLABORATIVE ANALYSIS OF INDIVIDUAL PATIENT DATA FROM THE FRISC II, ICTUS, AND RITA-3 TRIALS (FIR)


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ABSTRACT

Objectives: This study sought to investigate long-term outcomes after early or delayed angiography in patients with non-ST-elevation acute coronary syndrome (NSTE-ACS) undergoing a routine invasive management.

Background: The optimal timing of angiography in patients with NSTE-ACS is currently a topic for debate.

Methods: Long-term follow-up after early (within 2 days) angiography versus delayed (within 3 to 5 days) angiography was investigated in the FRISC-II, ICTUS and RITA-3 (FIR) NSTE-ACS patient-pooled database. The main outcome was cardiovascular death or myocardial infarction up to 5-year follow-up. Hazard ratios (HR) were calculated with Cox regression models. Adjustments were made for the FIR risk score, study and the propensity of receiving early angiography using inverse probability weighting.

Results: Of a total of 2721 patients originally randomized to the routine invasive arm, consisting of routine angiography and subsequent revascularization if suitable, 975 underwent early angiography and 1141 delayed angiography. No difference was observed in 5-year cardiovascular death or MI in unadjusted (HR 1.06, 95% CI 0.79-1.42, P=0.61) and adjusted (HR 0.93, 95% CI 0.75-1.16, P=0.54) Cox regression models.

Conclusion: In the FIR database of patients presenting with NSTE-ACS, the timing of angiography was not related to long-term cardiovascular mortality or MI.
INTRODUCTION

The routine invasive strategy and selective invasive strategy are alternative treatment strategies for patients presenting with non-ST-elevation acute coronary syndrome (NSTE-ACS). With the exception of indications for emergency angiography and revascularization, controversy remains about the optimal timing of angiography of those selected to undergo a routine invasive strategy. The American College of Cardiology (ACC)/American Heart Association (AHA) guidelines propose two approaches within the routine invasive strategy; early (including immediate) angiography or deferred angiography. Early angiography might timely identify those with left main or multivessel disease, expediting coronary artery bypass surgery (CABG), or lesions suitable for percutaneous coronary intervention (PCI). In addition, expediting intervention may reduce anti-thrombotic treatment use and the accompanying increased risk of bleeding. By contrast, deferred angiography might prevent procedure-related events after intensive anti-thrombotic and anti-ischemic therapy.

In two recent large randomized clinical trials, an early invasive strategy has been compared with a deferred invasive strategy. The Timing of Intervention in Acute Coronary Syndromes (TIMACS) trial showed that overall, a routine early-intervention strategy (coronary angiography within 24 hours) was not superior to a delayed-intervention strategy (angiography after 36 hours) for the prevention of the composite of death, myocardial infarction (MI) or stroke at six months. In the Angioplasty to Blunt the Rise of Troponin in Acute Coronary Syndromes Randomized for an Immediate or Delayed Intervention (ABOARD) trial, where an immediate angiography (“primary PCI approach”) was compared with delayed angiography, no difference was observed in the composite of death, MI, or urgent revascularisation at one month. However, both trials showed a benefit in high-risk patients. Several smaller randomised trials and posthoc analyses of randomised trials have shown inconsistent results regarding the timing of angiography or intervention. Furthermore, data on long-term follow-up is lacking.

We performed a collaborative analysis of data from the FRISC II, ICTUS, and RITA-3 trials of patients with NSTE-ACS to assess the effect of timing of angiography in patients originally randomized to the routine invasive strategy on the occurrence of long-term clinical outcomes. By pooling individual patient data, the effect of timing of angiography can adjusted for variables associated with timing of angiography and outcomes.

METHODS

Setting and data collection

The principal investigators (LW, RJdW, KAF) initiated this collaborative analysis, and a protocol was written summarizing the main prespecified analyses and a common set of variables. Investigators from the three trials provided individual patient data to form a patient-pooled database. The database included core
variables on demographics, clinical history, risk factors for coronary artery disease, baseline electrocardiographic characteristics, laboratory results and 5-year clinical outcomes. Data-sets 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 published previously. These trials compared a routine invasive strategy with a selective invasive strategy in patients with NSTE-ACS. 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 revascularization when appropriate. In the FRISC II trial, the aim was to perform angiography and revascularization, 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 revascularization 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.

**Timing of angiography**

For our current analyses, we included data from all patients originally randomized to the routine invasive strategy who underwent angiography. Patients undergoing a selective invasive management were excluded. Two study groups were formed; the early angiography group consisted of patients receiving coronary angiography on the day of randomization (day 1) or the next day and the delayed angiography group consisted of patients receiving coronary angiography within day three to five. A second analysis consisted of the time to angiography divided into 1-day intervals (from 1 day up to 5 days and a remaining group including angiography after 5 days or no angiography).

**Outcomes**

The main outcomes for the current analysis were the 5-year composite outcome cardiovascular (CV) death or MI and the individual 5-year outcomes CV death and MI. CV death was defined as all-cause death, unless an unequivocal noncardiovascular cause could be established. The original definition of MI per trial was used; readjudication of individual events to accommodate common definitions was not possible. MI in the FRISC II trial 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. MI in the RITA-3 trial 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. MI in the ICTUS trial was
declared 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 \(^{13}\).

Data concerning major bleeding was collected in 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 fatal, intracerebral hemorrhage or transfusion of 2 or more units.

**Statistical analysis**

Data with a normal distribution are described as the mean (with standard
deviation), data with a non-normal distribution as the median (with interquartile
range). The Student t test or a 1-way analysis of variance was used to compare
data with a normal distribution, whereas a nonparametric Kruskal-Wallis test
was used to compare data with a non-normal distribution. Categorical data are
presented as frequencies (%) and compared with a chi-square test. The primary
analysis was the comparison between patients who received angiography within
two days of randomization and those for which angiography was performed three
to five days after randomization regarding the composite outcome of CV death
or MI. Cumulative event rates for unadjusted analyses were estimated using 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. To adjust for the non-randomized allocation of the
timing of angiography, the relation of timing to CV death or MI was investigated
with the use of Cox proportional-hazards regression using inverse probability
weighting (IPW) \(^{15}\). IPW aims to reweight the observations such that the timing
of angiography becomes independent of measured confounders. We considered
the following baseline and angiographic characteristics as potential confounders
for the effect of timing on CV death or MI: study, age, gender, body mass index
(BMI), current smoking, hypertension, hyperlipidemia, diabetes mellitus, history
of MI or revascularization and the presence of ST-segment depression. For the
construction of IPW weights, we selected those variables that showed a relevant
association with the timing in logistic regression models (variables with a P-value
>0.1 by the likelihood ratio test were excluded from the model using backwards
selection). On top of the IPW correction we adjusted the Cox models for relevant
predictors of CV death or MI summarized in the FIR risk score, and for original
study \(^{16}\). Patients who did not receive angiography within one of the timeframes
used in the primary analysis were not part of that analysis. We also performed
landmark analyses, in which patients who received angiography within a 1-day
landmark were compared with all patients who received angiography after the
landmark or no angiography at all. Patients with events or angiography before
the landmark were excluded. The relation of timing of angiography in 1-day

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\(^{13}\) 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.

\(^{15}\) IPW aims to reweight the observations such that the timing of angiography becomes independent of measured confounders.

\(^{16}\) Patients who did not receive angiography within one of the timeframes used in the primary analysis were not part of that analysis.
intervals to CV death or MI was investigated with the use of Cox proportional-hazards regression in two sets of landmark models: models adjusted for relevant predictors of CV death or MI and study and models with adjustments for predictors of the timing angiography using IPW. Regarding IPW, we identified predictors for angiography within each landmark compared with later or no angiography.

Prespecified secondary analyses included comparisons of outcomes in the early (two days) versus delayed (three to five days) angiography groups 1) Interaction between timing of angiography and baseline risk as indicated by the FIR low-risk, intermediate-risk and high-risk categories \(^{16}\), 2) stratified by angiographic left main or three vessel disease and 3) restricted to patients that underwent intervention (PCI or CABG) within 30 days. The proportional hazards assumption for all analyses were verified graphically by checking parallelism of log-log survival curves and with Schoenfeld's tests, no relevant violations were observed.

**RESULTS**

**Patients**

A total of 2721 patients were originally randomized to the routine invasive arm, of which 244 had missing angiography data. Regarding the early and delayed study groups, 975 patients underwent early angiography (randomization day 1 or day 2) and 1141 patients underwent delayed angiography (day 3 to day 5). Of the remaining patients 317 underwent angiography later than five days and 44 underwent no angiography one at all. The latter two groups could only be used in the landmark analyses. The baseline characteristics of patients in the early and delayed angiography groups and in 1-day groups are shown in Table 1 and 2 respectively.

Patients undergoing early angiography more often had a history of PCI or CABG, more often were smokers or had hypercholesterolemia and were younger. Most patients in the early angiography group were originally from the ICTUS trial.

**Interventions**

During initial hospitalization, 654 (67%) patients were revascularized in the early angiography and 732 (64%) patients in the delayed angiography group (\(P=0.16\)). In the early angiography group, PCI was the first procedure 477 (73%) patients, CABG in 175 (27%) patients. Two patients received both on one day. In the delayed angiography group, these numbers were respectively 438 (60%), 292 (40%) and 2 (0%). The median time to first revascularization procedure during initial hospitalization was 1 day (IQR 1 to 5) in the early angiography and 4 days (IQR 3 to 6) in the delayed angiography group (\(P<0.001\)).

**Outcomes**

At a median of 5-year follow-up, early angiography did not result in a lower cumulative (unadjusted) CV death or MI rate compared with delayed angiography (15.4% versus 14.8%, \(P=0.61\)). Moreover, no differences in event rates were observed in the individual outcomes CV death (\(P=0.94\)) or MI (\(P=0.37\)). Divided
FIR TIMING OF ANGIOGRAPHY

into 1-day intervals or angiography after five days / no angiography at all, no difference was observed in the cumulative CV death or MI rate (log-rank P=0.61), CV death rate (log-rank P=0.95), or MI rate (log-rank P=0.21). The unadjusted Kaplan-Meier event rates are presented in Table 3. While awaiting angiography, six patients endured a spontaneous MI. Of these six MIs, three occurred on day 0, one on day 2 and two on day 3.

In unadjusted Cox proportional-hazards models, early angiography showed a similar CV death or MI hazard (HR 1.06, 95% CI 0.79-1.42, P=0.61), when compared with the delayed angiography group. After adjustment for the FIR risk score, study and IPW, no difference was observed when comparing the early angiography group with the delayed angiography group (HR 0.93, 95% CI 0.75-1.16, P=0.54). Moreover, no difference was observed regarding the individual outcomes. These

### Table 1. Baseline characteristics of the study patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Timing of angiography</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early (n=975)</td>
<td>Delayed (n=1141)</td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years) - median (IQR)</td>
<td>63 (55–71)</td>
<td>66 (57–72)</td>
</tr>
<tr>
<td>Body-mass index - mean (SD)</td>
<td>27.1 (4.0)</td>
<td>27.2 (4.0)</td>
</tr>
<tr>
<td>Male sex - no. (%)</td>
<td>675 (69%)</td>
<td>780 (68%)</td>
</tr>
<tr>
<td>History - no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>253 (26%)</td>
<td>294 (26%)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>96 (10%)</td>
<td>47 (4%)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>56 (6%)</td>
<td>5 (0%)</td>
</tr>
<tr>
<td>Risk factors - no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current cigarette smoking</td>
<td>354 (36%)</td>
<td>320 (28%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>335 (34%)</td>
<td>377 (33%)</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>303 (31%)</td>
<td>229 (20%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>135 (14%)</td>
<td>168 (15%)</td>
</tr>
<tr>
<td>ST-segment depression ≥0.1mV</td>
<td>401 (42%)</td>
<td>459 (40%)</td>
</tr>
<tr>
<td>FIR risk score*</td>
<td>5 (3–7)</td>
<td>5 (3–8)</td>
</tr>
<tr>
<td>Study</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FRISC II</td>
<td>117 (12%)</td>
<td>654 (57%)</td>
</tr>
<tr>
<td>ICTUS</td>
<td>540 (55%)</td>
<td>50 (4%)</td>
</tr>
<tr>
<td>RITA-3</td>
<td>318 (33%)</td>
<td>437 (38%)</td>
</tr>
</tbody>
</table>

CABG : coronary artery bypass grafting, IQR : interquartile range, PCI : percutaneous coronary intervention, SD : standard deviation
Early defined as angiography on day 1 (randomization) or 2, delayed on day 3 to 5
*FIR risk score calculated as : age: <60 years=0 score, 60 to 64 years=1, 65 to 69 years=2, 70 to 74 years=3, and ≥75 years=5; diabetes=4; hypertension=1; ST-segment depression=2; body mass index: <25 kg/m²=1, 25 to <35 kg/m²=0, ≥35 kg/m²=2.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Early angiography</th>
<th>Delayed angiography</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1 (n=281)</td>
<td>Day 2 (n=694)</td>
<td></td>
</tr>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years) - median (IQR)</td>
<td>63 (55–71)</td>
<td>63 (55–70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body-mass index - mean (SD)</td>
<td>27.0 (3.6)</td>
<td>27.2 (4.1)</td>
<td>0.94</td>
</tr>
<tr>
<td>Male sex - no. (%)</td>
<td>197 (70%)</td>
<td>478 (69%)</td>
<td>0.65</td>
</tr>
<tr>
<td>History - no.(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>65 (23%)</td>
<td>188 (27%)</td>
<td>0.73</td>
</tr>
<tr>
<td>PCI</td>
<td>41 (15%)</td>
<td>55 (8%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CABG</td>
<td>26 (9%)</td>
<td>30 (4%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Risk factors - no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current cigarette smoking</td>
<td>104 (37%)</td>
<td>250 (36%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>96 (34%)</td>
<td>239 (34%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>99 (35%)</td>
<td>204 (29%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>40 (14%)</td>
<td>95 (14%)</td>
<td>0.50</td>
</tr>
<tr>
<td>ST-segment depression ≥0.1mV</td>
<td>105 (39%)</td>
<td>296 (43%)</td>
<td>0.55</td>
</tr>
<tr>
<td>FIR risk score</td>
<td>5 (3–7)</td>
<td>5 (3–7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Study</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FRISC II</td>
<td>9 (3%)</td>
<td>108 (16%)</td>
<td></td>
</tr>
<tr>
<td>ICTUS</td>
<td>225 (80%)</td>
<td>315 (45%)</td>
<td></td>
</tr>
<tr>
<td>RITA-3</td>
<td>47 (17%)</td>
<td>271 (39%)</td>
<td></td>
</tr>
</tbody>
</table>

CABG: coronary artery bypass grafting, IQR: interquartile range, PCI: percutaneous coronary intervention, SD: standard deviation

P-value for overall comparison
results were consistent when assessed per individual trial. Regarding timing of angiography and FIR risk score, no interaction was observed (P for interaction in unadjusted and adjusted analyses respectively 0.98 and 0.89). The unadjusted and adjusted Cox models are shown in Table 4. Kaplan-Meier survival curves and adjusted hazard ratios are presented in Figure 1.

In the 1-day interval Cox proportional-hazards models adjusted for the FIR score and study or predictors for timing of angiography using IPW, angiography within none of the time intervals was associated with an increased CV death or MI hazard when compared with later on no angiography. The landmark models are shown in Figure 2.

**Early versus delayed angiography in revascularized patients**

In a separate analysis, we compared long-term outcomes between patients in the early and delayed angiography groups who underwent intervention within 30 days. In the early angiography and delayed angiography groups, respectively 666 and 763 patients were revascularized. No difference was observed between 30
Table 3. Unadjusted estimates of five-year outcomes according to time to angiography.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time to angiography</th>
<th>Time to angiography</th>
<th>P value</th>
<th>Time to angiography</th>
<th>Time to angiography</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early</td>
<td>Delayed</td>
<td></td>
<td>Day 1</td>
<td>Day 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Within 2 days</td>
<td>3-5 days</td>
<td>P value</td>
<td>Day 3</td>
<td>Day 4</td>
<td>Day 5</td>
</tr>
<tr>
<td>CV death or MI</td>
<td>(n=975)</td>
<td>(n=1141)</td>
<td></td>
<td>(n=281)</td>
<td>(n=694)</td>
<td>(n=479)</td>
</tr>
<tr>
<td>CV death</td>
<td>148 (15.4)</td>
<td>167 (14.8)</td>
<td>0.61</td>
<td>39 (14.0)</td>
<td>109 (15.9)</td>
<td>70 (14.8)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>61 (6.4)</td>
<td>71 (6.3)</td>
<td>0.94</td>
<td>15 (5.4)</td>
<td>46 (6.8)</td>
<td>28 (5.9)</td>
</tr>
<tr>
<td></td>
<td>105 (11.0)</td>
<td>111 (10.0)</td>
<td>0.37</td>
<td>29 (10.5)</td>
<td>76 (11.2)</td>
<td>46 (8.9)</td>
</tr>
</tbody>
</table>

CV : cardiovascular, MI : myocardial infarction
P-value by log-rank test for overall comparison
Table 4. Hazard ratios for long-term outcomes comparing early with delayed angiography.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Unadjusted model</th>
<th>Adjusted model*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>CV death or MI</td>
<td>1.06 (0.79 – 1.42)</td>
<td>0.61</td>
</tr>
<tr>
<td>CV death or MI</td>
<td>P for interaction</td>
<td>0.98†</td>
</tr>
<tr>
<td>FIR low-risk group</td>
<td>1.34 (0.75 – 2.40)</td>
<td>0.97</td>
</tr>
<tr>
<td>FIR intermediate-risk group</td>
<td>0.90 (0.56 – 1.45)</td>
<td>0.70</td>
</tr>
<tr>
<td>FIR high-risk group</td>
<td>1.14 (0.69 – 1.89)</td>
<td>1.14</td>
</tr>
<tr>
<td>CV death</td>
<td>1.01 (0.65 – 1.59)</td>
<td>0.94</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.13 (0.80 – 1.61)</td>
<td>0.37</td>
</tr>
</tbody>
</table>

*Adjusted for FIR score (continuous variable), study and inverse probability of treatment weight.
†P-value for interaction between timing of angiography and FIR risk score
CV : cardiovascular, FIR : FRISC II – ICTUS – RITA-3, MI : myocardial infarction

Figure 2. Landmark analyses for the composite of CV death or MI. Patients undergoing angiography within each landmark are compared with patients undergoing angiography at a later time point or no angiography at all. For example, the HR next to day 1 is for comparison day 1 versus day 2 or later. Patients with events before angiography are excluded. Multivariable landmark analyses are adjusted for the FIR score and study. Inverse probability of treatment landmark analyses are weighted for predictors of receiving angiography within a landmark. MI : myocardial infarction.
days and the end of follow-up regarding CV death (P=0.59). Kaplan-Meier curves for CV death are shown in Figure 3.

**Major bleeding**

Data concerning major bleeding during initial hospitalization was collected in the ICTUS and RITA-3 trials. In the early angiography arm, 28 of 857 patients (3.3%) endured a major bleeding. This was not significantly different when compared with 15 of the 486 patients (3.1%) who endured a major bleeding in the delayed angiography arm (P=0.86).

**Left main or three vessel disease**

In the ICTUS and RITA-3 trials, data was collected during coronary angiography. Of 1461 patients with known angiography data, 343 were diagnosed as having a ≥50% stenosis in the left main or in three major epicardial arteries (≥50% in other arteries then the left main). Within this subgroup, comparable CV death or MI rates were observed between early or delayed angiography (19.6% versus 12.0%, P=0.09). These event rates were respectively 13.6% and 12.8% in patients without left main or three vessel disease (P=0.62).

**DISCUSSION**

Several implications can be drawn from the current FIR patient-pooled analysis. First, early angiography within 2 days was not associated with lower 5-year CV death or MI when compared with delayed angiography within three to five days. There were no differences in individual long-term CV death or MI rates. These results were consistent after adjustment for predictors for long-term outcomes, study and predictors for timing of angiography. In 1-day interval landmark analyses, angiography within any of the time intervals was not associated with an increased CV death or MI hazard compared with later angiography or no angiography at all.

**Previous studies**

In the earlier mentioned TIMACS and ABOARD trials, no difference was shown in clinical outcomes when comparing an early angiography with a delayed angiography treatment strategy. However, the TIMACS and ABOARD trials demonstrated no difference at short-term outcomes (six months and one month respectively) when comparing a very early or immediate angiography, while our data concerns angiography within 2 days compared with later angiography. We note that a benefit of early angiography was observed in high-risk patients in both TIMACS and ABOARD. We did not observe an interaction between timing of angiography and baseline risk profile as indicated by the FIR risk score.

In the smaller ISAR-COOL trial, patients were randomized to expedited angiography (within 6 hours) or to a strategy of three to five days of prolonged antithrombotic treatment followed by angiography. An excessive event rate incurred during antithrombotic pretreatment in the prolonged pretreatment
arm, resulting in a significant benefit in 30-day death or MI with the expedited angiography strategy. We did not observe this excessive hazard with increasing times to angiography in our data. Few patients endured a spontaneous MI while awaiting angiography or subsequent revascularization.

In a subanalysis of the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY) trial, PCI after 24 hours was associated with 1-year mortality and adverse ischemic outcomes. The highest hazard was observed in high-risk patients, as identified by the Thrombolysis In Myocardial Infarction (TIMI) risk score. It is not possible to directly compare our current analysis with these results, because we investigated time to angiography instead of time to PCI. Potentially, medically stabilized patients undergoing delayed angiography do not undergo PCI and are thus excluded from time to PCI analyses. Moreover, patients referred for CABG are also excluded. We explored the relation between time to PCI and outcomes in our early versus delayed study group, and did not observe a significant

![Figure 3. Kaplan-Meier curves for CV death after revascularization according to timing of angiography. Event rates are Kaplan-Meier estimates. P-value by the log-rank test. CV: cardiovascular.](image)
difference in unadjusted event rates when comparing patients undergoing early versus delayed PCI (data not shown).

In both the TIMACS and ACUITY substudy, the Kaplan-Meier estimates or curves for mortality continue to diverge up to 30 days and thereafter. Apparently, the risk of delaying angiography and subsequent intervention extends to the period after the intervention. However, when we compared early with delayed angiography in patients who underwent revascularization within 30 days, no difference in CV mortality was observed. Because outcomes after revascularization can be expected to be similar and potential mechanisms for late mortality are not elucidated in the previously mentioned studies, further studies are required to confirm our findings.

Bleeding
Major bleeding has been identified as an independent predictor of mortality. Patients in the delayed angiography group receive a prolonged medical treatment with antiplatelet and antithrombin agents, potentially placing them at a higher bleeding risk. However, the duration of antiplatelet and antithrombin administration did not influence major bleeding in the ACUITY trial. This is supported by the results of the TIMACS and ABOARD trials, where no differences in major bleedings were observed. In our current analysis, no difference in major bleeding was observed when comparing early angiography with delayed angiography. Furthermore, we did not observe any difference in mortality between the timing study groups.

Left main or three vessel disease
According to the ACC/AHA guidelines, patients with left main coronary artery disease or multivessel disease are candidates for expedited CABG in order to avoid a risky waiting period. In our current analyses suggest that CV death or MI rates in these patients were comparable with early angiography or delayed angiography. However, one should be cautious when interpreting subgroup analyses, albeit prespecified.

Clinical implications and future perspectives
Because we did not observe a relation between timing of angiography and outcomes, a potential implication could be that angiography can be postponed to the next working day in patients presenting outside working-hours. On the other side, early angiography might potentially reduce hospitalization time and associated costs. Keeping limitations of a post-hoc analysis in mind, these findings should be interpreted as hypothesis generating. Furthermore, future research should focus on the patients at highest baseline risk and cost-effectiveness analyses. Finally, the current analysis does not address the appropriateness of the very early compared with immediate angiography.

Limitations
Our study has some limitations. Patients were not randomized to have coronary angiography within a particular time from randomization, and therefore, differences
in outcomes may reflect differences in patient characteristics or practice patterns rather than differences in time to coronary angiography. One of these differences might be the number of patients that required urgent angiography because of severe ongoing angina, profound or dynamic ECG changes, major arrhythmias or hemodynamic instability. Although we corrected for important predictors of CV death or MI, study and predictors for receiving angiography, our results could have been biased by unavailable variables such as stent placement and cardiac biomarkers. 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 allow for a more accurate assessment of the effect of timing of angiography on the clinical outcome MI. This limitation should be taken into account in the 1-day analysis where there is a varying contribution of MIs to the combined outcome. Third, cardiac biomarkers rise, peak and decline over time relative to the onset of myocardial ischemia, and an additional biomarker increase due to an early procedure is difficult to distinguish from already elevated biomarker levels due to the index event. In the ICTUS trial, patients were eligible if they were troponin positive, recurrent MI during the first 48 hours was diagnosed when there was a 50 percent decrease from a previous peak biomarker value, followed by a subsequent rise to a level exceeding the ULN as measured by routine serial sampling. The detection of procedure-related MI might thus be prone to detection bias, especially in the early angiography group. However the procedure-related MIs were adjudicated by a clinical endpoint committee.

CONCLUSION

We conclude that in patients presenting with NSTE-ACS, early angiography within 48 hours does not reduce the incidence of 5-year death or MI, when compared with delayed angiography within 48 to 120 hours.

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REFERENCE LIST


