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## Early Invasive versus Selectively Invasive Management for Acute Coronary Syndromes

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### ABSTRACT

#### BACKGROUND

Current guidelines recommend an early invasive strategy for patients who have acute coronary syndromes without ST-segment elevation and with an elevated cardiac troponin T level. However, randomized trials have not shown an overall reduction in mortality, and the reduction in the rate of myocardial infarction in previous trials has varied depending on the definition of myocardial infarction.

#### METHODS

We randomly assigned 1200 patients with acute coronary syndrome without ST-segment elevation who had chest pain, an elevated cardiac troponin T level ( $\geq 0.03$   $\mu\text{g}$  per liter), and either electrocardiographic evidence of ischemia at admission or a documented history of coronary disease to an early invasive strategy or to a more conservative (selectively invasive) strategy. 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 was recommended. The primary end point was a composite of death, nonfatal myocardial infarction, or rehospitalization for anginal symptoms within one year after randomization.

#### RESULTS

The estimated cumulative rate of the primary end point was 22.7 percent in the group assigned to early invasive management and 21.2 percent in the group assigned to selectively invasive management (relative risk, 1.07; 95 percent confidence interval, 0.87 to 1.33;  $P=0.33$ ). The mortality rate was the same in the two groups (2.5 percent). Myocardial infarction was significantly more frequent in the group assigned to early invasive management (15.0 percent vs. 10.0 percent,  $P=0.005$ ), but rehospitalization was less frequent in that group (7.4 percent vs. 10.9 percent,  $P=0.04$ ).

#### CONCLUSIONS

We could not demonstrate that, given optimized medical therapy, an early invasive strategy was superior to a selectively invasive strategy in patients with acute coronary syndromes without ST-segment elevation and with an elevated cardiac troponin T level.

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**P**ATIENTS WITH ACUTE CORONARY SYNDROMES without ST-segment elevation are at risk for adverse cardiac events.<sup>1</sup> Optimal treatment consists of intensive medical therapy followed by diagnostic coronary angiography and revascularization in some patients. In five large, randomized trials (Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital [VANQWISH], Fragmin and Fast Revascularization during Instability in Coronary Artery Disease [FRISC II], Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy—Thrombolysis in Myocardial Infarction 18 [TACTICS-TIMI 18], TIMI IIIB, and the Third Randomized Intervention Treatment of Angina [RITA-3]), a routine, early invasive strategy (early angiography followed by revascularization, depending on angiographic findings) was compared with a “conservative” strategy (angiography and subsequent revascularization only if medical therapy failed or substantial residual ischemia was documented).<sup>2-6</sup> An early invasive strategy was shown to be beneficial in the FRISC II, TACTICS-TIMI 18, and RITA-3 studies, especially in subgroups of patients at high risk, such as those presenting with an elevated cardiac troponin level. As a result, recent guidelines of the American College of Cardiology–American Heart Association and the European Society of Cardiology recommend an early invasive approach in high-risk patients with acute coronary syndromes without ST-segment elevation.<sup>7,8</sup>

Despite these recommendations, it is not clear that an early invasive strategy reduces mortality in this setting. A reduction in mortality was shown in the FRISC II study, but only among men. Such a reduction was not seen in any of the other studies. In addition, the reduction in the incidence of myocardial infarction associated with an early invasive strategy in these studies depended on the definition of myocardial infarction. Moreover, recent advances in medical therapy, such as the early use of clopidogrel and intensive lipid-lowering therapy, have been shown to improve the prognosis in patients with acute coronary syndromes.<sup>9,10</sup> These therapies have not been tested in trials of early invasive strategies. Therefore, we conducted the present study to test the hypothesis that an early invasive strategy is superior to a selectively invasive strategy for patients who have acute coronary syndromes without ST-segment elevation and with an elevated cardiac troponin T level.

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## METHODS

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### STUDY POPULATION AND STUDY DESIGN

Between July 2001 and August 2003, 1200 patients were enrolled from 42 Dutch hospitals, 12 of which were high-volume centers with facilities for percutaneous coronary intervention and on-site cardiac surgery. The protocol was approved by all the local institutional review boards. All patients gave written informed consent. The trial was funded by a combination of sources. The sponsors had no involvement in the design of the study, data collection or analysis, or the writing of the manuscript.

Eligible patients had to have all three of the following: symptoms of ischemia that were increasing or occurred at rest, with the last episode occurring no more than 24 hours before randomization; an elevated cardiac troponin T level ( $\geq 0.03$   $\mu\text{g}$  per liter); and either ischemic changes as assessed by electrocardiography (defined as ST-segment depression or transient ST-segment elevation exceeding 0.05 mV, or T-wave inversion of  $\geq 0.2$  mV in two contiguous leads) or a documented history of coronary artery disease as evidenced by previous myocardial infarction, findings on previous coronary angiography, or a positive exercise test. Exclusion criteria were an age younger than 18 years or older than 80 years, myocardial infarction with ST-segment elevation in the past 48 hours, an indication for primary percutaneous coronary intervention or fibrinolytic therapy, hemodynamic instability or overt congestive heart failure, the use of oral anticoagulant drugs in the past 7 days, fibrinolytic treatment within the past 96 hours, percutaneous coronary intervention within the past 14 days, a contraindication to treatment with percutaneous coronary intervention or glycoprotein IIb/IIIa inhibitors, recent trauma or risk of bleeding, hypertension despite treatment (i.e., systolic pressure  $>180$  mm Hg or diastolic pressure  $>100$  mm Hg), weight greater than 120 kg, or inability to give informed consent.

### OPTIMIZED MEDICAL THERAPY

The protocol specified that patients receive 300 mg of aspirin at the time of randomization, followed by at least 75 mg daily indefinitely, and enoxaparin (1 mg per kilogram of body weight, to a maximum of 80 mg) twice daily subcutaneously for at least 48 hours. Patients already started on unfraction-

ated heparin were switched to enoxaparin immediately after randomization. The early use of clopidogrel (300 mg immediately, followed by 75 mg daily) in combination with aspirin was recommended to the investigators after the drug was approved in 2002 for the indication of acute coronary syndromes.<sup>9</sup>

All interventional procedures during the initial hospital phase were performed with the use of abciximab, given as a bolus dose of 0.25 mg per kilogram, followed by an infusion of 0.125 µg per kilogram per minute for 12 hours, and started 10 to 60 minutes before the first balloon inflation.<sup>11</sup> Abciximab was also available for use in patients who subsequently underwent percutaneous revascularization. The protocol recommended intensive lipid-lowering therapy, preferably 80 mg of atorvastatin daily or the equivalent, started as soon as possible after randomization and continued indefinitely. The level of the MB isoform of creatine kinase (CK-MB) was measured at 6-hour intervals during the first period of 24 hours or more after admission, after each new clinical episode of ischemia, and after each percutaneous revascularization procedure.

#### TREATMENT STRATEGY

Patients were randomly assigned to an early invasive strategy or a selectively invasive strategy with the use of a central telephone system. Permuted-block randomization was performed, with stratification according to site, with block size randomly chosen to be four, six, or eight. Patients assigned to the early invasive strategy were scheduled to undergo angiography within 24 to 48 hours after randomization and percutaneous coronary intervention when appropriate on the basis of the coronary anatomy. Coronary-artery bypass grafting was recommended in patients with extensive three-vessel disease or severe left main-stem disease and was to be performed as soon as possible during the initial hospitalization period.

Patients assigned to the selectively invasive strategy were treated medically. These patients were scheduled to undergo angiography and subsequent revascularization only if they had refractory angina despite optimal medical treatment, hemodynamic or rhythmic instability, or clinically significant ischemia on the predischarge exercise test. Coronary angiography and revascularization after the initial hospital phase were performed if severe anginal symptoms (i.e., Canadian Cardiovascular Society

[CCS] class III or IV) persisted despite optimal antianginal medication or if ischemia was documented on subsequent testing. Follow-up outpatient visits occurred at 1, 6, and 12 months after randomization.

#### END POINTS

The primary end point was a composite of death, recurrent myocardial infarction, or rehospitalization for angina within one year after randomization. Death was defined as death from any cause. Myocardial infarction was defined as documented myocardial necrosis, occurring either spontaneously or in the setting of percutaneous intervention, according to the recommendations of the Joint European Society of Cardiology–American College of Cardiology Committee for the Redefinition of Myocardial Infarction.<sup>12</sup> Myocardial necrosis was defined by an elevation in the CK-MB level above the upper limit of normal. In the event of an elevated CK-MB level at randomization, recurrent myocardial infarction during the first 48 hours was diagnosed when there was a 50 percent decrease from a previous peak value, followed by a subsequent rise to a level exceeding the upper limit of normal. A myocardial infarction in the setting of coronary-artery bypass grafting required the occurrence of electrocardiographic evidence of new Q waves.

Major bleeding not related to coronary-artery bypass grafting during the index admission was defined by at least one of the following: fatal bleeding, intracranial bleeding, a need for blood transfusion, a decrease of 3 mmol per liter (4.8 g per deciliter) or more in hemoglobin levels, and bleeding resulting in hemodynamic compromise. All end points were adjudicated by members of an independent clinical end-points committee, who were unaware of the treatment assignments of the patients.

#### STATISTICAL ANALYSIS

We calculated that, given a 21 percent incidence of the primary end point in the group assigned to an early invasive strategy, 1200 patients would be needed to provide the study with 80 percent power to detect a relative risk reduction of 25 percent between the two groups, at an alpha level of 0.05. Continuous variables with normal distributions are expressed as means ±SD and were compared with the use of an unpaired Student's *t*-test. Categorical variables were compared with the use of Fisher's

**Table 1. Baseline Characteristics of the Patients.\***

| Characteristic  | Early Invasive Strategy (N=604) | Selectively Invasive Strategy (N=596) |
|---|---------------------------------|---------------------------------------|
| Age — yr  |                                 |                                       |
| Median  | 62                              | 62                                    |
| Range   | 29–81                           | 30–83                                 |
| Age ≥65 yr — no. (%)  | 263 (44)                        | 266 (45)                              |
| Male sex — no. (%)  | 446 (74)                        | 434 (73)                              |
| Body-mass index†  | 27±4                            | 27±4                                  |
| Clinical history — no. (%)  |                                 |                                       |
| Myocardial infarction   | 153 (25)                        | 125 (21)                              |
| Percutaneous coronary intervention                                    | 77 (13)                         | 63 (11)                               |
| Coronary-artery bypass grafting                                       | 62 (10)                         | 43 (7)                                |
| Risk factors — no. (%)  |                                 |                                       |
| Hypertension  | 226 (37)                        | 240 (40)                              |
| Diabetes mellitus   | 86 (14)                         | 80 (13)                               |
| Hypercholesterolemia  | 211 (35)                        | 206 (35)                              |
| Current cigarette smoking   | 244 (40)                        | 248 (42)                              |
| Family history of coronary artery disease                             | 263 (44)                        | 241 (40)                              |
| Known left ventricular ejection fraction <35%                         | 10 (2)                          | 7 (1)                                 |
| Medications at admission — no. (%)                                    |                                 |                                       |
| Aspirin   | 235 (39)                        | 221 (37)                              |
| Angiotensin-converting-enzyme inhibitors                              | 88 (15)                         | 82 (14)                               |
| Beta-blockers   | 220 (36)                        | 196 (33)                              |
| Calcium-channel antagonists   | 92 (15)                         | 96 (16)                               |
| Nitrates  | 70 (12)                         | 64 (11)                               |
| Statins   | 172 (28)                        | 157 (26)                              |
| Time from onset of symptoms to randomization — hr                     | 17±10                           | 17±9                                  |
| Electrocardiographic evidence of abnormalities at admission — no. (%) |                                 |                                       |
| ST-segment deviation ≥0.1 mV  | 284 (47)                        | 290 (49)                              |
| Isolated T-wave inversion   | 48 (8)                          | 44 (7)                                |
| Electrocardiogram missing or unreadable                               | 26 (4)                          | 25 (4)                                |
| Cardiac troponin T level‡   |                                 |                                       |
| <0.10 µg/liter  | 108 (18)                        | 110 (18)                              |
| 0.10–0.29 µg/liter  | 199 (33)                        | 195 (33)                              |
| 0.30–0.99 µg/liter  | 186 (31)                        | 186 (31)                              |
| ≥1.0 µg/liter   | 111 (18)                        | 105 (18)                              |

\* Differences between the treatment groups were not statistically significant. Plus-minus values are means ±SD.

† Body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Cardiac troponin T levels were measured at the clinical chemistry core laboratory on the Elecsys 2010 system (Roche Diagnostics, Germany).

exact test or the chi-square test, where appropriate. All reported P values are two-sided and not adjusted for multiple testing.

Event rates at one year were estimated with the Kaplan–Meier method.<sup>13</sup> Relative risks were calculated by dividing the Kaplan–Meier estimated rate of an event at one year in the early-invasive-strategy group by that in the group assigned to a selectively invasive strategy. The 95 percent confidence interval for the relative risk was calculated with the use of the standard errors from the Kaplan–Meier curve. The significance of differences in event rates between treatment groups was assessed with the use of the log-rank test. Data on patients who were lost to follow-up were censored at the time of the last contact.

## RESULTS

A total of 604 patients were randomly assigned to the early invasive strategy and 596 patients to the selectively invasive strategy. Baseline characteristics are shown in Table 1. The median age was 62 years, about three quarters of the patients were male, and 14 percent had diabetes. Cardiac catheterization was performed during the initial hospitalization in 98 percent of patients in the early-invasive-strategy group and 53 percent in the selectively-invasive-strategy group, and in 99 percent and 67 percent, respectively, within one year (Table 2). Within one year, 79 percent of the patients in the early-invasive-strategy group had undergone revascularization, as compared with 54 percent in the selectively-invasive-strategy group. Eighty-eight percent of the percutaneous coronary intervention procedures in both treatment groups combined involved the placement of at least one stent. Medical therapy at discharge was similar between the group assigned to an early invasive strategy and the group assigned to a selectively invasive strategy, except for the use of clopidogrel (61 percent vs. 49 percent, respectively). The incidence of statin use at discharge was very high in both groups (90 percent and 94 percent, respectively).

## PRIMARY END POINT

Six patients were lost to follow-up before one year. A total of 263 patients (137 patients in the early-invasive-strategy group and 126 patients in the selectively-invasive-strategy group) reached the primary end point. Kaplan–Meier curves for the primary end point are shown in Figure 1. The estimat-

**Table 2. Cardiac Procedures within Two Days after Randomization, during Initial Hospitalization, and within One Year, According to Study Group.**

| Procedure                           | Within Two Days                 |                                       | During Initial Hospitalization  |                                       | Within One Year                 |                                       |
|-------------------------------------|---------------------------------|---------------------------------------|---------------------------------|---------------------------------------|---------------------------------|---------------------------------------|
|                                     | Early Invasive Strategy (N=604) | Selectively Invasive Strategy (N=596) | Early Invasive Strategy (N=604) | Selectively Invasive Strategy (N=596) | Early Invasive Strategy (N=604) | Selectively Invasive Strategy (N=596) |
|                                     | <i>number (percent)</i>         |                                       |                                 |                                       |                                 |                                       |
| Catheterization                     | 588 (97)                        | 64 (11)                               | 593 (98)                        | 314 (53)                              | 597 (99)                        | 397 (67)                              |
| Percutaneous coronary intervention* | 321 (53)                        | 22 (4)                                | 361 (60)                        | 169 (28)                              | 371 (61)                        | 239 (40)                              |
| Coronary-artery bypass grafting     | 15 (2)                          | 1 (<1)                                | 97 (16)                         | 68 (11)                               | 107 (18)                        | 85 (14)                               |
| Revascularization                   | 336 (56)                        | 23 (4)                                | 458 (76)                        | 237 (40)                              | 478 (79)                        | 324 (54)                              |

\* The median time to percutaneous coronary intervention was 23 hours (25th to 75th percentile, 15 to 44) in the early-invasive-strategy group and 283 hours (25th to 75th percentile, 142 to 647) in the group assigned to a selectively invasive strategy. During initial hospitalization, procedures involving percutaneous coronary intervention were performed, accompanied by the use of abciximab, in 94 percent of patients undergoing percutaneous coronary intervention in the early-invasive-strategy group and 75 percent of those undergoing percutaneous coronary intervention in the selectively-invasive-strategy group. Within one year after randomization, 93 percent and 69 percent of procedures, respectively, involving percutaneous coronary intervention were performed, accompanied by the use of abciximab.

ed one-year cumulative event rate was 22.7 percent in the early-invasive-strategy group and 21.2 percent in the group assigned to a selectively invasive strategy (relative risk, 1.07; 95 percent confidence interval, 0.87 to 1.33; P=0.33) (Table 3). One-year mortality was 2.5 percent in both groups (relative risk, 0.99; 95 percent confidence interval, 0.49 to 2.00; P=0.97). The cumulative risk of myocardial infarction within one year after randomization was significantly higher in the early-invasive-strategy group (15.0 percent vs. 10.0 percent; relative risk, 1.50; 95 percent confidence interval, 1.10 to 2.04; P=0.005). Rehospitalization was less frequent in the early-invasive-strategy group (7.4 percent vs. 10.9 percent; relative risk, 0.68; 95 percent confidence interval, 0.47 to 0.98; P=0.04).

Several baseline clinical features were examined for potential effects in a subgroup analysis. The relative risks were not different among the major subgroups defined according to age, sex, the presence or absence of diabetes mellitus, the presence or absence of ST-segment deviation, or the level of cardiac troponin T (Fig. 2).

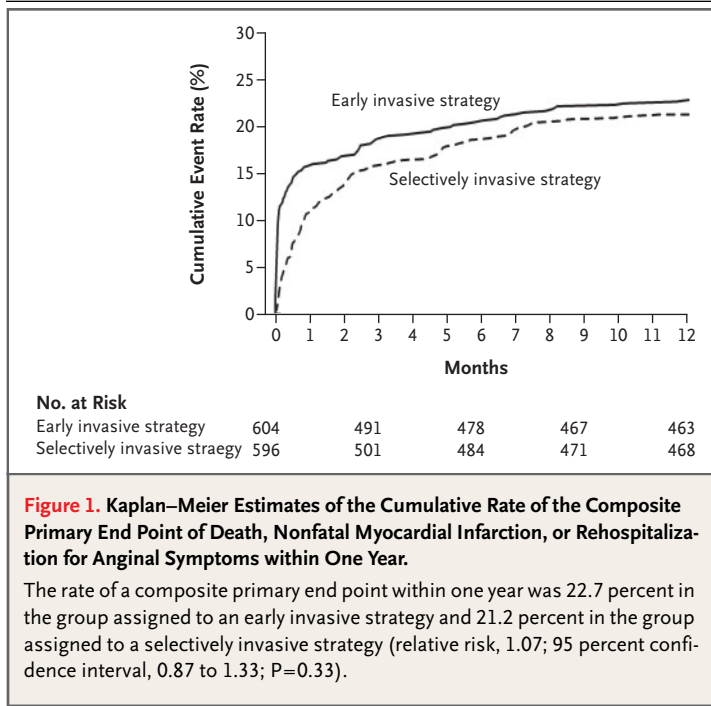
**MYOCARDIAL INFARCTION**

Categories of infarct size according to peak CK-MB level are shown in Table 3. The rate of myocardial infarction among patients with a peak CK-MB level one to three times the upper limit of normal was

significantly higher in the early-invasive-strategy group than in the group assigned to a selectively invasive strategy (7.2 percent vs. 4.6 percent, P=0.05). The incidence of myocardial infarction related to percutaneous coronary intervention or coronary-artery bypass grafting was also significantly higher in the early-invasive-strategy group (11.3 percent vs. 5.4 percent, P=0.001). To compare our results with those of previous trials, we applied the definitions of myocardial infarction from the FRISC II<sup>4</sup> and the TACTICS-TIMI 18<sup>5</sup> studies to our data (Table 3). Applying these definitions lowered the rate of infarction. However, the relative risks remained essentially unaltered, and there were no significant differences in the rate of the composite primary end point between the groups, irrespective of the definition of infarction applied.

**OTHER SECONDARY END POINTS**

The percentage of patients free from anginal symptoms was similar in the early-invasive-strategy group and the group assigned to a selectively invasive strategy (86 percent and 87 percent, respectively). Moreover, the incidence of angina, defined as CCS class I to IV, was similar in the two groups (data not shown). Major bleeding not related to coronary-artery bypass grafting during the index admission occurred in 19 patients (3.1 percent) in the early-invasive-strategy group, as compared with



10 patients (1.7 percent) in the group assigned to a selectively invasive strategy.

## DISCUSSION

This study did not show that an early invasive strategy was superior to a selectively invasive strategy in patients who had an acute coronary syndrome without ST-segment elevation and who had an elevated cardiac troponin T level. Mortality within one year was low (2.5 percent in both groups), despite the fact that these patients were all considered at high risk. The incidence of myocardial infarction was significantly higher in the early-invasive-strategy group, particularly during hospitalization, confirming the finding of the FRISC II researchers<sup>4</sup> that there is an early hazard associated with early revascularization. The incidence of the primary end point was 22.7 percent in the early-invasive-strategy group, but 21.2 percent in the group assigned to a selectively invasive strategy, which was lower than anticipated. There was no significant difference in the frequency of the primary end point among subgroups defined according to age, sex, the presence or absence of diabetes mellitus, the presence or absence of ST-segment deviation, or the level of cardiac troponin T.

Comparing the results of the present study with

those of previous trials is not straightforward, owing to differences in study design, in the risk profile of patients included, in antithrombotic therapy, and in the definition of end points, in particular the definition of myocardial infarction; changes in the practice of invasive therapy (especially the use of stents and glycoprotein IIb/IIIa inhibitors); and the observed contrast between strategies in the rate and timing of revascularization. There are several possible explanations for the observed differences in outcome between the present study and previous trials.

First, revascularization rates were high in the two groups in our study (76 percent in the early-invasive-strategy group and 40 percent in the selectively-invasive-strategy group during the initial hospitalization, and 79 percent and 54 percent, respectively, within 1 year after randomization) as compared with those in TIMI-IIIb (64 percent vs. 58 percent at 1 year), VANQWISH (44 percent vs. 33 percent at 23 months), FRISC II (71 percent vs. 9 percent at 10 days, and 77 percent vs. 37 percent at 6 months), TACTICS-TIMI 18 (61 percent vs. 44 percent at 6 months), and RITA-3 (44 percent vs. 10 percent during the index admission, and 57 percent vs. 28 percent within 1 year).<sup>14</sup> As in the VANQWISH trial, all patients in our study had evidence of myocardial necrosis, as compared with 58 percent with an elevated troponin level in FRISC II, 54 percent in TACTICS-TIMI 18, and 75 percent in RITA-3. The fact that all patients in the present study were at high risk (as evidenced by an elevated troponin level) may explain the earlier and more frequent revascularization in the group assigned to a selectively invasive strategy in our study. The 40 percent rate of revascularization during the initial hospitalization in the group assigned to a selectively invasive strategy in our study compares well with the 48 percent rate of revascularization in patients with acute coronary syndromes who were admitted to centers with catheterization facilities in the global registry of acute coronary events (the GRACE registry), which reflects real-world clinical practice.<sup>15</sup>

Second, as in FRISC II, most myocardial infarctions in the early-invasive-strategy group in our study were procedure-related.<sup>16</sup> The higher incidence of myocardial infarction in this group is driven in large part by relatively small infarctions related to percutaneous coronary intervention that were detected with carefully timed and frequent measurements of CK-MB levels. Moreover, we applied the Joint European Society of Cardiology–

**Table 3. Cumulative Rate of the Composite Primary End Point and Its Components within One Year after Randomization.\***

| Outcome  | Early Invasive Strategy (N=604) |           | Selectively Invasive Strategy (N=596) |           | Relative Risk (95% CI) | P Value |
|--|---------------------------------|-----------|---------------------------------------|-----------|------------------------|---------|
|  | no.                             | rate (%)† | no.                                   | rate (%)† |                        |         |
| Death  | 15                              | 2.5       | 15                                    | 2.5       | 0.99 (0.49–2.00)       | 0.97    |
| Myocardial infarction‡   | 90                              | 15.0      | 59                                    | 10.0      | 1.50 (1.10–2.04)       | 0.005   |
| Peak CK-MB ≥1 to <3×ULN  | 43                              | 7.2       | 27                                    | 4.6       | 1.57 (0.98–2.51)       | 0.05    |
| Peak CK-MB ≥3 to <5×ULN  | 15                              | 2.5       | 7                                     | 1.2       | 2.09 (0.86–5.10)       | 0.09    |
| Peak CK-MB ≥5 to <10×ULN   | 14                              | 2.3       | 13                                    | 2.2       | 1.06 (0.50–2.23)       | 0.86    |
| Peak CK-MB ≥10×ULN   | 11                              | 1.8       | 6                                     | 1.0       | 1.79 (0.67–4.80)       | 0.23    |
| No CK-MB, new Q waves  | 7                               | 1.2       | 6                                     | 1.0       | 1.15 (0.39–3.37)       | 0.80    |
| Spontaneous  | 22                              | 3.7       | 27                                    | 4.6       | 0.80 (0.46–1.34)       | 0.45    |
| Related to percutaneous coronary intervention or coronary-artery bypass grafting | 68                              | 11.3      | 32                                    | 5.4       | 2.09 (1.39–3.14)       | 0.001   |
| FRISC II definition§   | 73                              | 12.1      | 46                                    | 7.8       | 1.56 (1.10–2.22)       | 0.008   |
| TACTICS–TIMI 18 definition¶  | 51                              | 8.5       | 35                                    | 5.9       | 1.43 (0.95–2.17)       | 0.07    |
| Rehospitalization for anginal symptoms   | 44                              | 7.4       | 64                                    | 10.9      | 0.68 (0.47–0.98)       | 0.04    |
| Primary composite end point  | 137                             | 22.7      | 126                                   | 21.2      | 1.07 (0.87–1.33)       | 0.33    |
| FRISC II definition§   | 122                             | 20.2      | 115                                   | 19.3      | 1.05 (0.83–1.32)       | 0.52    |
| TACTICS–TIMI 18 definition¶  | 102                             | 16.9      | 105                                   | 17.6      | 0.96 (0.75–1.23)       | 0.87    |

\* The tabulations of the composite primary end point include the first event — death, myocardial infarction, or rehospitalization — for each patient. The tabulations of component events include all such events (e.g., under the category “death,” all deaths are counted, including those that occurred after a hospitalization or a myocardial infarction). CI denotes confidence interval, ULN the upper limit of normal, FRISC II Fragmin and Fast Revascularization during Instability in Coronary Artery Disease II trial, and TACTICS–TIMI 18 the Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive Conservative Strategy–Thrombolysis in Myocardial Infarction 18 trial.

† The event rate within one year was determined with the use of the Kaplan–Meier curves.

‡ For the assessment of myocardial infarction, the level of the MB isoform of creatine kinase (CK-MB) was measured at 6-hour intervals during the first period of 24 hours or more after admission, after each new clinical episode of recurrent ischemia, and after each percutaneous revascularization procedure.

§ The FRISC II definition of myocardial infarction is a CK-MB level above the upper limit of normal for spontaneous myocardial infarction and more than 1.5 times the upper limit of normal for myocardial infarction related to percutaneous coronary intervention.

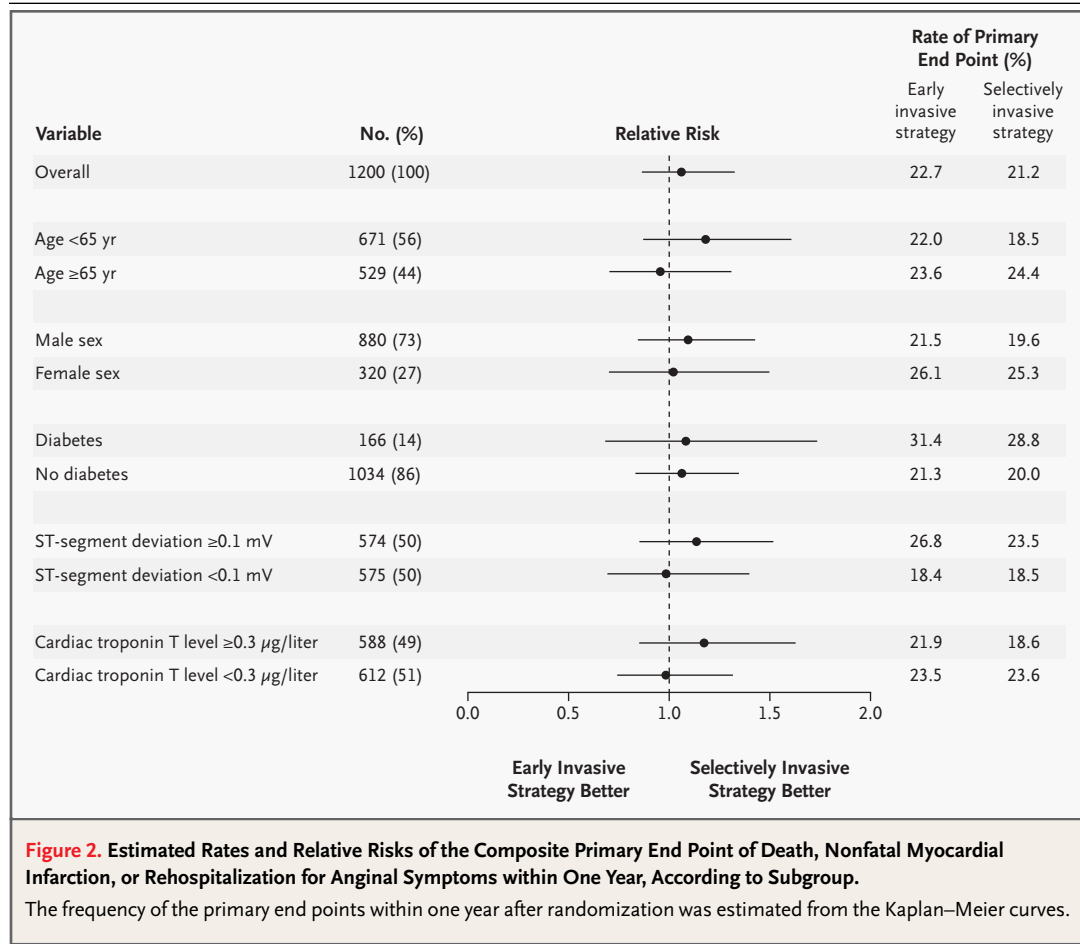
¶ The TACTICS–TIMI 18 definition of myocardial infarction is a CK-MB level above the upper limit of normal for spontaneous myocardial infarction or more than three times the upper limit of normal for myocardial infarction related to percutaneous coronary intervention.

American College of Cardiology definitions of spontaneous and percutaneous coronary intervention–related myocardial infarction (peak CK-MB level, greater than the upper limit of normal).<sup>12</sup> Different cutoff levels for infarctions related to percutaneous coronary intervention were used in FRISC II (CK-MB level, >1.5 times the upper limit of normal), TACTICS–TIMI 18 (CK-MB level, ≥3 times the upper limit of normal), and RITA-3 and Superior Yield of the New Strategy of Enoxaparin, Revascularization, and Glycoprotein IIb/IIIa Inhibitors (SYNERGY) (CK-MB level, 2 times the upper limit of normal). The incidence of myocardial in-

farction in the early-invasive-strategy group in our study (15.0 percent at 1 year; median time to percutaneous coronary intervention, 23 hours) was similar to that in the recent SYNERGY trial (11.7 percent at 30 days; median time to percutaneous coronary intervention, 23 hours), in which an early-intervention strategy was used.<sup>17</sup>

The prognostic implications of periprocedural myocardial damage are controversial, but some reports suggest that the prognosis of patients with such injury should be regarded as similar to that of patients with spontaneous necrosis.<sup>16,18,19</sup> To determine whether the increased incidence of pro-





cedure-related myocardial infarction in the early-invasive-strategy group in our study eventually results in a worse prognosis will require long-term follow-up. Regardless of the definition of myocardial infarction in our study, we could not demonstrate a significant difference in the incidence of the composite primary end point between the two treatment strategies.

Third, the incidence of myocardial infarction in the group assigned to a selectively invasive strategy was lower than expected. We incorporated recent advances in background medical therapy, such as the use of abciximab at the time of percutaneous coronary intervention procedures, the early use of clopidogrel, and intensive lipid-lowering therapy, which have been shown to improve outcomes in patients who have acute coronary syndromes without ST-segment elevation.<sup>10,20</sup> This may partially explain the lower-than-expected event rate in the group assigned to a selectively invasive strategy.

Finally, all procedures were performed in high-

volume centers with facilities for cardiac surgery on site, resulting in a low overall mortality, including a low mortality related to coronary-artery bypass grafting. In our view, advances in background medical therapy in combination with better detection of myocardial infarctions with frequent, carefully timed measurements of CK-MB levels best explain the differences between our results and those of previous trials.

The 2003 European Society of Cardiology guidelines were published during the study enrollment period. Physicians familiar with the guidelines would probably be inclined to favor performing angiography in most patients with an elevated cardiac troponin T level. As a result, physicians participating in our study might have enrolled lower-risk patients than would otherwise have been included. However, baseline characteristics suggest that we studied a high-risk population, with more than one third of the patients already taking aspirin, more than half having ischemic changes as as-

essed by electrocardiography, and all having an elevated cardiac troponin T level as confirmed with core laboratory analysis.

We did not find the expected 25 percent reduction in the cumulative rate of the primary end point with an early invasive strategy as compared with a selectively invasive strategy. As a result, the confidence interval around the relative risk of the composite end point of death, myocardial infarction, or rehospitalization for angina was 0.87 to 1.33, corresponding to a possible reduction in risk of 13 percent (or an increase in risk of 33 percent) with an early invasive strategy. However, the point estimate for the relative risk (1.07) actually favors the selectively invasive approach, and even the most substantial advantage of early invasive management consistent with our data is much less than that estimated in previous large trials.

Among patients with acute coronary syndromes without ST-segment elevation who have an elevated cardiac troponin T level, we could not demon-

strate that an early invasive strategy was superior to a selectively invasive strategy. These results were obtained with the use of contemporary medical therapy that included low-molecular-weight heparin, glycoprotein IIb/IIIa inhibition at the time of percutaneous procedures, clopidogrel, and intensive lipid-lowering therapy.

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APPENDIX

The following investigators and research coordinators, all in the Netherlands, participated in the ICTUS trial (total number of patients recruited are indicated in parentheses): *Academisch Medisch Centrum, Amsterdam* (105) — R.J.G. Peters; *Amphia Ziekenhuis, Breda* (101) — P.H.J.M. Dunselman; *Universitair Medisch Centrum St. Radboud, Nijmegen* (78) — F.W.A. Verheugt; *Westfries Gasthuis, Hoorn* (74) — C.L. Janus; *Medisch Centrum Alkmaar, Alkmaar* (72) — V. Umans; *Elkerliek Ziekenhuis, Helmond* (65) — P.E.F. Bendermacher; *Catharina Ziekenhuis, Eindhoven* (59) — H.R. Michels; *Flevoziekenhuis, Almere* (48) — A. Sadée; *Canisius-Wilhelmina, Nijmegen* (46) — D. Hertzberger; *Maasziekenhuis, Boxmeer* (40) — J. Peters; *Ziekenhuis Hilversum, Hilversum* (40) — P.A.R.M. de Miliano; *Oosterschelde Ziekenhuis, Goes* (38) — A.H. Liem; *Rijnstate Ziekenhuis, Arnhem* (38) — R. Tjon Joe Gin; *Christelijk Ziekenhuis Nij Smellinghe, Drachten* (36) — M. van der Linde; *Deventer Ziekenhuis, Deventer* (36) — D. Lok; *Ziekenhuis Gooi-Noord, Blaricum* (35) — G. Hoedemaker; *Boven IJ Ziekenhuis, Amsterdam* (28) — M. Pieterse; *Scheperziekenhuis, Emmen* (27) — L. van den Merkhof; *Jeroen Bosch Ziekenhuis, Den Bosch* (25) — M. Daniëls; *Groene Hart Ziekenhuis, Gouda* (20) — M. van Hessen; *St. Elisabeth Ziekenhuis, Tilburg* (19) — W. Hermans; *Slotervaart Ziekenhuis, Amsterdam* (18) — C.E. Schotborgh; *AZM, Maastricht* (18) — C. de Zwaan; *Diakonessenhuis, Utrecht* (17) — A. Bredero; *Universitair Medisch Centrum, Utrecht* (17) — P. de Jaegere; *Kenemer Gasthuis, Haarlem* (14) — M. Janssen; *Medisch Spectrum Twente, Enschede* (11) — J. Louwerenburg; *St. Franciscus, Rotterdam* (11) — M. Veerhoek; *LUMC, Leiden* (11) — M. Schalijs; *Gemini Ziekenhuis, Den Helder* (10) — A. de Porto; *UMCG, Groningen* (10) — F. Zijlstra; *Tweesteden Ziekenhuis, Tilburg* (10) — J. Winter; *Erasmus MC, Rotterdam* (8) — P. de Feyter; *Ziekenhuis Leyenburg Den Haag* (7) — R. Robles de Medina; *Reinier de Graaf Gasthuis, Delft* (6) — P. Withagen; *Bronovo Ziekenhuis, Den Haag* (5) — M. Sedney; *Maxima Medisch Centrum, Veldhoven* (4) — H. Thijssen; *Rijnland Ziekenhuis, Leiderdorp* (3) — C. van Rees; *Streekziekenhuis Zevenaar, Zevenaar* (2) — P. van den Bergh; *VUMC, Amsterdam* (1) — C. de Cock; *Isala klinieken, Zwolle* — A. van 't Hof; *St. Antonius Ziekenhuis, Nieuwegein* — M.J. Suttorp; *Trial Steering Committee* — R.J. de Winter (chair), F. Windhausen, J.H. Cornel, J.G.P. Tijssen, F.W.A. Verheugt, P.H.J.M. Dunselman, P.J. de Feyter, H.R. Michels; *Executive Committee* — R.J. de Winter, F. Windhausen, J.G.P. Tijssen; *End Point Adjudication Committee* — D. Düren, K. Liem; *Data Center and Monitoring* — Academisch Medisch Centrum, Amsterdam; *Clinical Chemistry Core Laboratory* — Academisch Medisch Centrum, Amsterdam, Laboratory of Clinical Chemistry, G.T.B. Sanders, J. Fischer, J. van Straalen.

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