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Early versus Delayed Invasive Intervention in Acute Coronary Syndromes

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ABSTRACT

BACKGROUND

Earlier trials have shown that a routine invasive strategy improves outcomes in patients with acute coronary syndromes without ST-segment elevation. However, the optimal timing of such intervention remains uncertain.

METHODS

We randomly assigned 3031 patients with acute coronary syndromes to undergo either routine early intervention (coronary angiography ≤ 24 hours after randomization) or delayed intervention (coronary angiography ≥ 36 hours after randomization). The primary outcome was a composite of death, myocardial infarction, or stroke at 6 months. A prespecified secondary outcome was death, myocardial infarction, or refractory ischemia at 6 months.

RESULTS

Coronary angiography was performed in 97.6% of patients in the early-intervention group (median time, 14 hours) and in 95.7% of patients in the delayed-intervention group (median time, 50 hours). At 6 months, the primary outcome occurred in 9.6% of patients in the early-intervention group, as compared with 11.3% in the delayed-intervention group (hazard ratio in the early-intervention group, 0.85; 95% confidence interval [CI], 0.68 to 1.06; $P=0.15$). There was a relative reduction of 28% in the secondary outcome of death, myocardial infarction, or refractory ischemia in the early-intervention group (9.5%), as compared with the delayed-intervention group (12.9%) (hazard ratio, 0.72; 95% CI, 0.58 to 0.89; $P=0.003$). Prespecified analyses showed that early intervention improved the primary outcome in the third of patients who were at highest risk (hazard ratio, 0.65; 95% CI, 0.48 to 0.89) but not in the two thirds at low-to-intermediate risk (hazard ratio, 1.12; 95% CI, 0.81 to 1.56; $P=0.01$ for heterogeneity).

CONCLUSIONS

Early intervention did not differ greatly from delayed intervention in preventing the primary outcome, but it did reduce the rate of the composite secondary outcome of death, myocardial infarction, or refractory ischemia and was superior to delayed intervention in high-risk patients. (ClinicalTrials.gov number, NCT00552513.)

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RANDOMIZED TRIALS HAVE SHOWN THAT a routine invasive strategy is beneficial in high-risk patients with acute coronary syndromes.¹⁻³ In patients with myocardial infarction with ST-segment elevation, in which the infarct-related artery is usually occluded and there is ongoing transmural ischemia, it is well established that the earlier primary percutaneous coronary intervention (PCI) can be performed, the lower the mortality.^{4,5} By contrast, in patients with acute coronary syndromes without ST-segment elevation (including unstable angina and myocardial infarction), the culprit artery is often patent, there is usually no ongoing transmural ischemia, and the patient often has a good response to initial medical treatment.⁶

Although a policy of routine intervention in such patients has been associated with an improved outcome,⁷⁻¹⁰ the optimal timing of such intervention has not been well established. Early intervention might prevent ischemic events that could occur while the patient is awaiting a delayed procedure.¹¹ Alternatively, by treating a patient with intensive antithrombotic therapy and delaying intervention for several days, procedure-related complications might be avoided with intervention on a more stable plaque.^{12,13} Thus, the question of when to intervene in patients with acute coronary syndromes without ST-segment elevation has not been definitively answered. Given this uncertainty, we designed a large, multicenter, randomized trial to determine whether the use of early coronary angiography and intervention was a superior approach to a delayed strategy.

METHODS

PATIENTS

The Timing of Intervention in Acute Coronary Syndromes (TIMACS) trial was a randomized, parallel-group, multicenter trial with blinded adjudication of outcomes. From April 2003 through June 2008, a total of 3031 patients underwent randomization. The trial began as an investigator-initiated, randomized substudy of the Fifth Organization to Assess Strategies in Ischemic Syndromes (OASIS-5) trial (ClinicalTrials.gov number, NCT00139815), from which the first 1633 patients were recruited, with an additional 1398 patients recruited after the main OASIS-5 trial had ended. The OASIS-5 trial was a study of 20,078

patients with unstable angina or myocardial infarction without ST-segment elevation who were randomly assigned to receive, in a double-blind, double-placebo fashion, either fondaparinux or enoxaparin in addition to other standard treatments. The design and results of the OASIS-5 trial have been reported previously.^{14,15}

Patients were eligible for the TIMACS study if they presented to a hospital with unstable angina or myocardial infarction without ST-segment elevation within 24 hours after the onset of symptoms and if they had two of the following three criteria indicative of increased risk: an age of 60 years or older, cardiac biomarkers above the upper limit of the normal range, or results on electrocardiography that were compatible with ischemia (i.e., ST-segment depression of ≥ 1 mm or transient ST-segment elevation or T-wave inversion of >3 mm). Patients were excluded if they were not suitable candidates for revascularization. Additional exclusion criteria are described in the Supplementary Appendix, available with the full text of this article at NEJM.org.

The trial was approved by the local institutional review board at each participating institution, and all patients provided written informed consent. The trial was coordinated by the Population Health Research Institute at McMaster University and Hamilton Health Sciences and was overseen by a steering committee of international experts.

RANDOMIZATION AND STUDY TREATMENTS

Permuted-block randomization, stratified according to study center, was performed with the use of a central 24-hour, computerized, toll-free interactive voice-response system located at the Population Health Research Institute. In order to maintain the usual practices at study centers, the principal investigator had the option to choose, in advance, one of the following randomization ratios for early intervention to delayed intervention: 1:1, 1:2, or 2:1.

Among patients who were randomly assigned to the early-intervention group, coronary angiography was to be performed as rapidly as possible and within 24 hours after randomization. Patients who were assigned to the delayed-intervention group underwent coronary angiography after a minimum delay of 36 hours after randomization. Revascularization was to be attempted in the two groups if at least one major coronary artery had

substantial stenosis or occlusion, provided that the attending physician deemed that the coronary anatomy was suitable for PCI or coronary-artery bypass grafting (CABG). For patients in the early-intervention group, revascularization was to occur as soon as possible after coronary angiography. For patients in the delayed-intervention group, revascularization could occur at any time after coronary angiography. Blood was drawn for analysis of the creatine kinase MB fraction and troponin level before revascularization and at 6 to 8 hours and at 12 to 14 hours after revascularization. Electrocardiography was performed 12 to 18 hours after revascularization.

The selection of the mode of revascularization (PCI or CABG) was based on patients' characteristics and preferences, the extent of disease, the presence or absence of coexisting illnesses, and the level of left ventricular function. Protocol criteria for crossover from the delayed-intervention group to the early-intervention group and recommended pharmacologic therapies are described in the Supplementary Appendix.

PRIMARY AND SECONDARY OUTCOMES

The primary outcome was the first occurrence of the composite of death, new myocardial infarction, or stroke at 6 months. The two secondary outcomes were the first occurrence of the composite of death, myocardial infarction, or refractory ischemia and the composite of death, myocardial infarction, stroke, refractory ischemia, or repeat intervention at 6 months. Other outcomes included each of the individual components analyzed separately. (See the Supplementary Appendix for definitions of outcome events.)

STATISTICAL ANALYSIS

With a sample size of 3000 patients, the trial had a power of 80% to detect a reduction of 28% in the relative risk of the primary outcome of death, myocardial infarction, or stroke, assuming an event rate of 11% in the delayed-intervention group and a two-tailed type I error of 5%. On the basis of the same assumptions and at a power of 80%, an enrollment of 4000 patients would have allowed the detection of a reduction of 24.9% in the relative risk. Because of recruitment challenges, the steering committee decided to cap the study enrollment at 3000 patients. All patients were included in the final intention-to-treat analysis, regardless of which treatment they actually

received. Event rates in the two groups were estimated with the use of the Kaplan–Meier method. The hazard ratio and two-sided 95% confidence intervals were calculated with the use of a Cox proportional-hazards model, with the study group as the only covariate. In consideration of the potential for confounding by the assignment ratio, stratified Cox proportional-hazards analyses were performed on the primary outcome, with the assignment ratio treated as a stratum. The prespecified subgroup analyses included age (<65 years or ≥65 years), sex, the presence or absence of diabetes, the presence or absence of ST-segment changes, cardiac-marker positivity at baseline, and risk according to the Global Registry of Acute Coronary Events (GRACE) risk score,¹⁶ stratified into thirds. The GRACE risk score (on a scale of 1 to 372, with higher scores indicating greater risk) is derived from readily available hospital admission variables, including age, heart rate, systolic blood pressure, creatinine level, Killip class, cardiac arrest at admission, presence of ST-segment deviation, and elevated cardiac biomarkers. Values for these variables can be entered into the GRACE risk calculator (available at www.outcomes.org/grace) to derive a prognostic score that will estimate the risk of death or the combined risk of death or myocardial infarction at 6 months in individual patients. Additional statistical analyses and tests for interaction are described in the Supplementary Appendix.

RESULTS

PATIENTS

Of the 3031 patients in the study, 1593 were randomly assigned to the early-intervention group and 1438 to the delayed-intervention group. Complete follow-up was obtained for 99.7% of patients in the early-intervention group and for 99.9% of patients in the delayed-intervention group. Baseline characteristics were well matched between the two groups. The use of evidence-based therapies, including aspirin, thienopyridines, angiotensin-converting-enzyme inhibitors, and statins, was high and similar in the two groups (Table 1).

Overall, 97.6% of patients in the early-intervention group underwent coronary angiography (median time after randomization, 14 hours), as compared with 95.7% in the delayed-intervention group (median time, 50 hours) (Table 1). The rates of PCI were slightly higher in the early-inter-

Table 1. Baseline Characteristics of the Patients, Medications, and Interventions after Randomization.*			
Variable	Early Intervention (N=1593)	Delayed Intervention (N=1438)	P Value
Demographic characteristic			
Age (yr)	65.0	65.7	0.28
Female sex (%)	34.8	34.6	0.92
Medical history (%)			
Diabetes	26.5	27.4	0.58
Previous myocardial infarction	19.7	20.9	0.41
Previous stroke	7.2	7.5	0.71
Ischemic changes on ECG	80.5	79.9	0.69
Elevated cardiac biomarker	77.2	76.9	0.84
Previous coronary procedure (%)			
PCI	13.9	14.2	0.81
CABG	7.0	7.3	0.73
In-hospital medication (%)			
Aspirin	98.0	98.1	0.90
Thienopyridine	87.2	86.7	0.66
Clpidogrel			
Loading dose of 300 mg before PCI	81.0	85.7	<0.001
Loading dose of 600 mg before PCI	9.8	6.9	0.009
Glycoprotein IIb/IIIa inhibitor	23.2	22.4	0.61
Thienopyridine or glycoprotein IIb/IIIa inhibitor	88.2	88.4	0.87
Anticoagulant†	97.0	97.0	1.00
Heparin			
Unfractionated	24.6	24.7	0.97
Low-molecular-weight	64.6	63.9	0.70
Fondaparinux	41.3	41.8	0.81
Bivalirudin	0.4	0.5	0.85
Beta-blocker	86.8	86.9	0.93
Statin	85.1	84.3	0.56
Angiotensin-converting-enzyme inhibitor	74.2	73.6	0.70
Extent of coronary disease			
Left main artery	10.0	9.5	0.70
No. of vessels involved			
1	31.6	31.1	
2	24.5	23.4	
3	17.1	15.8	
Interventions after randomization			
Coronary angiography (%)	97.6	95.7	0.003
Median time (hr)	14	50	<0.001
Interquartile range (hr)	3–21	41–81	
PCI (%)	59.6	55.1	0.01
Median time (hr)	16	52	<0.001
Interquartile range (hr)	3–23	41–101	
CABG (%)	14.8	13.6	0.56
Median time (days)	7.7	10.8	<0.001
Interquartile range (days)	4.7–17.4	6.7–19.8	

* CABG denotes coronary-artery bypass grafting, ECG electrocardiography, and PCI percutaneous coronary intervention.
† Patients may have received more than one anticoagulant.

vention group (59.6%) than in the delayed-intervention group (55.1%), as were the rates of CABG (14.8% vs. 13.6%). Of patients who were assigned to the early-intervention group, 9.9% underwent coronary angiography more than 24 hours after randomization, whereas 20.5% of patients who were assigned to the delayed-intervention group underwent coronary angiography less than 36 hours after randomization.

PRIMARY AND SECONDARY OUTCOMES

At 6 months, the primary outcome (death, new myocardial infarction, or stroke) occurred in 9.6% of patients in the early-intervention group, as compared with 11.3% in the delayed-intervention group (hazard ratio in the early-intervention group, 0.85; 95% confidence interval [CI], 0.68 to 1.06; $P=0.15$) (Table 2 and Fig. 1A). There was no significant difference between the early-intervention group and the delayed-intervention group in the rate of death (4.8% vs. 5.9%), new myocardial in-

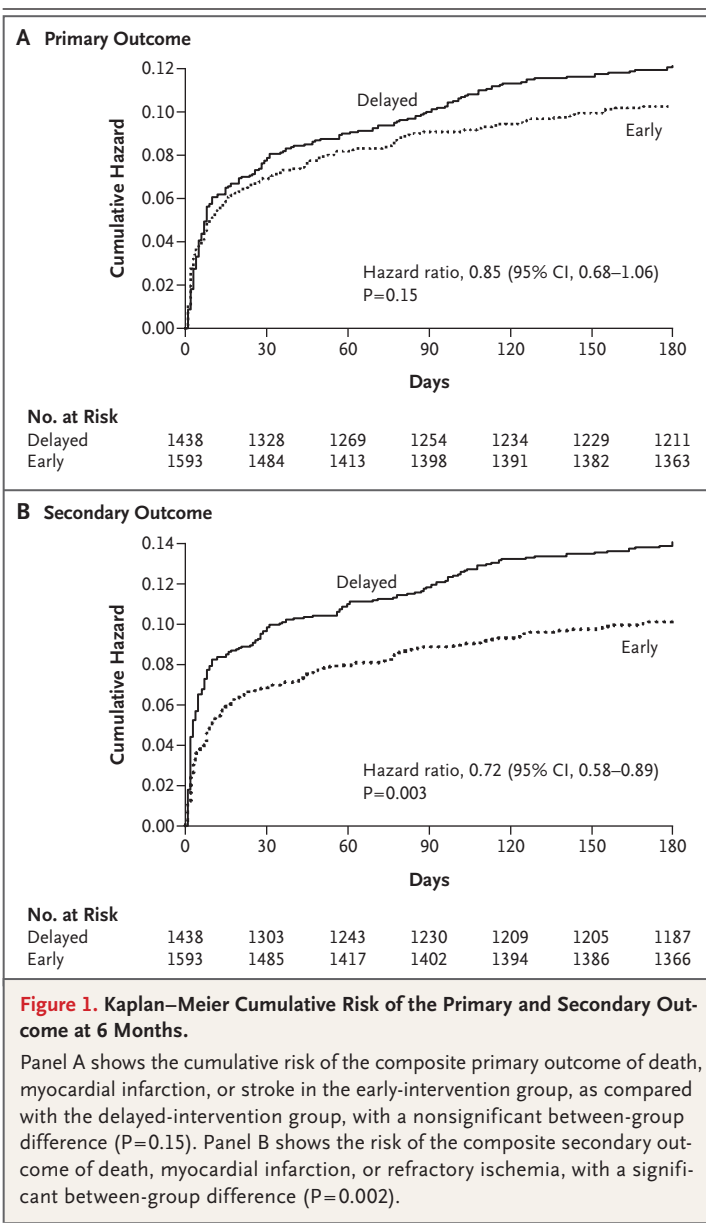
farction (4.8% vs. 5.7%), and stroke (1.3% vs. 1.4%) (Table 2). When the primary outcome was adjusted for the assignment ratio used during randomization, similar results to the main analysis were observed (hazard ratio, 0.84; 95% CI, 0.67 to 1.05; $P=0.13$).

The secondary outcome of death, myocardial infarction, or refractory ischemia at 6 months occurred in 9.5% of patients in the early-intervention group, as compared with 12.9% in the delayed-intervention group (hazard ratio, 0.72; 95% CI, 0.58 to 0.89; $P=0.003$) (Table 2 and Fig. 1B). This difference was attributed mainly to a large reduction in refractory ischemia favoring early intervention (1.0% vs. 3.3%; hazard ratio, 0.30; 95% CI, 0.17 to 0.54; $P<0.001$). Among patients who had an episode of refractory ischemia, the subsequent risk of myocardial infarction was increased by a factor of more than 4, with a rate of 20.6% among those with refractory ischemia, as compared with 4.8% among those without

Table 2. Primary and Secondary Outcomes.*

Variable	Early Intervention (N=1593)	Delayed Intervention (N=1438)	Hazard Ratio (95% CI)	P Value
<i>percent</i>				
At 6 mo				
Death, myocardial infarction, or stroke	9.6	11.3	0.85 (0.68–1.06)	0.15
Death, myocardial infarction, or refractory ischemia	9.5	12.9	0.72 (0.58–0.89)	0.003
Death, myocardial infarction, stroke, refractory ischemia, or repeat intervention	16.6	19.5	0.84 (0.71–0.99)	0.04
Death	4.8	5.9	0.81 (0.60–1.11)	0.19
Myocardial infarction	4.8	5.7	0.83 (0.61–1.14)	0.25
Stroke	1.3	1.4	0.90 (0.49–1.68)	0.74
Refractory ischemia	1.0	3.3	0.30 (0.17–0.54)	<0.001
Repeat intervention	8.7	8.5	1.04 (0.82–1.34)	0.73
At 30 days				
Death, myocardial infarction, or stroke	6.7	7.6	0.88 (0.67–1.15)	0.34
Death, myocardial infarction, or refractory ischemia	6.6	9.3	0.70 (0.54–0.90)	0.006
Death, myocardial infarction, stroke, refractory ischemia, or repeat intervention	12.0	13.0	0.91 (0.75–1.12)	0.37
Death	2.9	3.3	0.86 (0.58–1.29)	0.48
Myocardial infarction	3.6	4.1	0.87 (0.61–1.25)	0.46
Stroke	0.9	0.9	1.04 (0.50–2.19)	0.91
Refractory ischemia	1.0	3.1	0.30 (0.17–0.55)	<0.001
Repeat intervention	5.9	4.2	1.39 (1.01–1.93)	0.05

* Hazard ratios are for the comparison between the early-intervention group and the delayed-intervention group.



refractory ischemia (hazard ratio, 4.6; 95% CI, 2.6 to 8.2; $P<0.001$). The other secondary outcome of death, myocardial infarction, stroke, refractory ischemia, or repeat intervention also significantly favored the early-intervention group at 6 months (Table 2). Although the rate of repeat intervention was slightly higher in the early-intervention group at 30 days (5.9% vs. 4.2%, $P=0.046$), it did not differ significantly between groups at 6 months (8.7% vs. 8.5%, $P=0.73$). Similarly, the rate of heart failure did not differ significantly between the two groups at 6 months (5.3% vs. 5.7%; hazard ratio, 0.93; $P=0.64$).

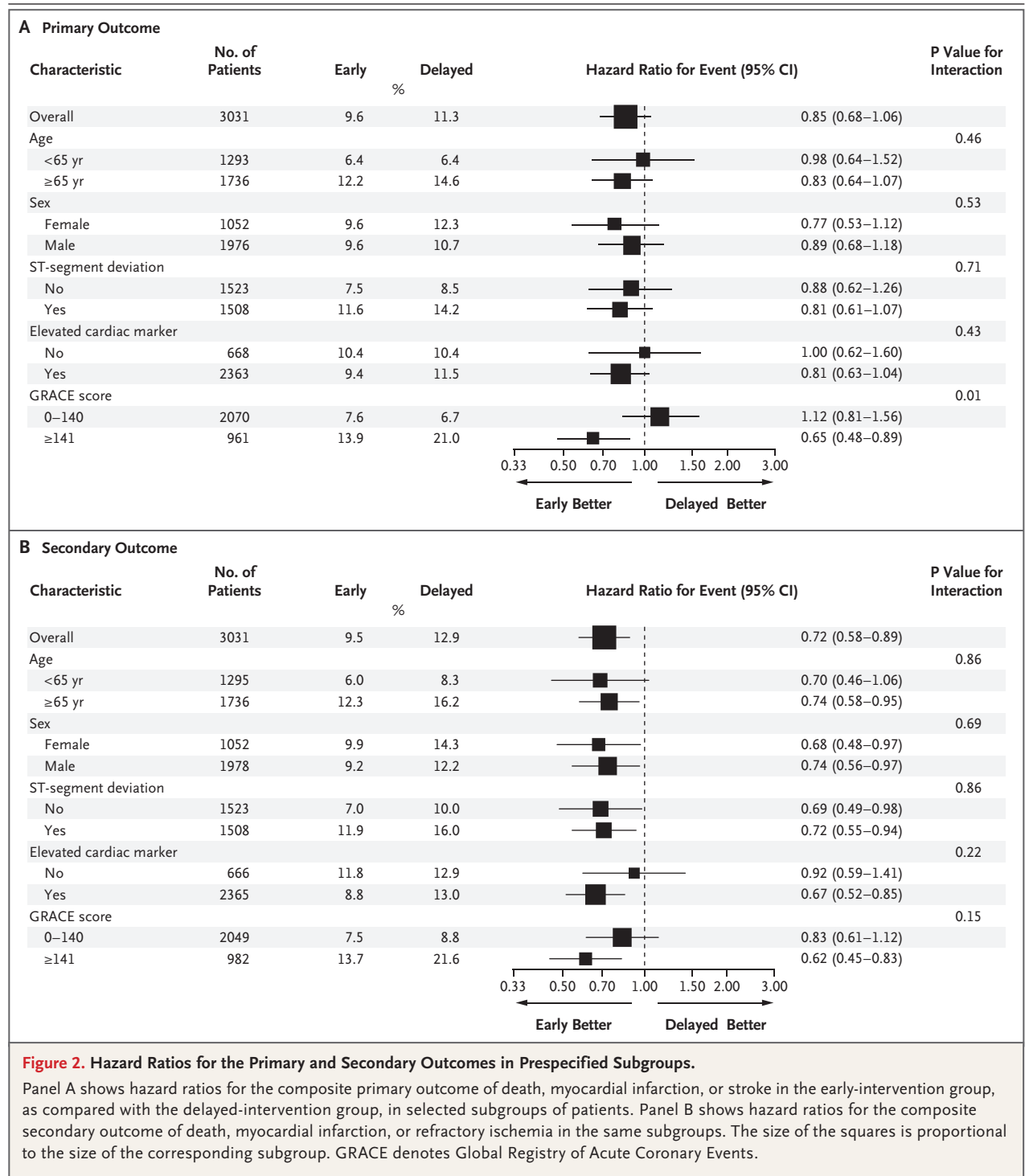
SAFETY OUTCOMES

A major bleeding event occurred in 3.1% of patients in the early-intervention group, as compared with 3.5% in the delayed-intervention group (hazard ratio, 0.89; 95% CI, 0.60 to 1.31; $P=0.55$). There was no significant difference between the early-intervention group and the delayed-intervention group in the rate of intracranial hemorrhage (none vs. 0.1%), the need for surgical intervention to stop bleeding (0.4% vs. 0.8%), retroperitoneal hemorrhage (0.1% vs. 0.2%), a decrease in hemoglobin of 3 g per deciliter or more (2.3% vs. 2.6%), and transfusion of 2 or more units of blood (2.2% vs. 2.9%).

PRESPECIFIED SUBGROUPS

There was no significant heterogeneity in primary or secondary outcomes in subgroups stratified according to age, sex, or the presence or absence of ST-segment deviation or elevation in cardiac biomarkers at trial entry (Fig. 2). However, there was significant heterogeneity when the primary outcome was stratified into thirds according to baseline risk (Fig. 3). In patients with a GRACE risk score of more than 140 (the third with the highest risk), the primary outcome occurred in 13.9% of patients in the early-intervention group, as compared with 21.0% in the delayed-intervention group, a reduction of 35.0% in the early-intervention group (hazard ratio, 0.65; 95% CI, 0.48 to 0.89; $P=0.006$). However, among patients with a score of 140 or less (a combination of the low-risk and intermediate-risk thirds), there was no significant difference between groups (7.6% vs. 6.7%; hazard ratio, 1.12; 95% CI, 0.81 to 1.56; $P=0.48$; $P=0.01$ for heterogeneity) (Fig. 3). Similarly, among high-risk patients, the secondary composite outcome of death, myocardial infarction, or refractory ischemia occurred in 13.7% of patients in the early-intervention group, as compared with 21.6% in the delayed-intervention group (hazard ratio, 0.62; 95% CI, 0.45 to 0.83; $P=0.002$). In patients at low-to-intermediate risk, the secondary outcome was more modestly reduced (7.5% vs. 8.8%; hazard ratio, 0.83; 95% CI, 0.61 to 1.12; $P=0.23$).

In exploratory analyses, we found no significant heterogeneity in the primary outcome or the secondary outcome of death, myocardial infarction, or refractory ischemia among study centers in which the median time to coronary angiography in the early-intervention group was less than



6 hours, 6 to 12 hours, or more than 12 hours (see the Supplementary Appendix for details). Consistent outcomes were also observed in patients undergoing PCI or CABG after randomization (Table 1 in the Supplementary Appendix).

DISCUSSION

The principal findings of our study are that in patients with acute coronary syndromes without ST-segment elevation, an early-intervention strat-

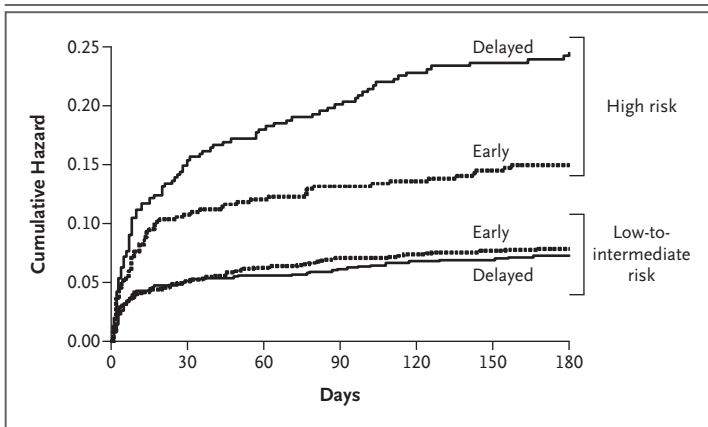


Figure 3. Kaplan–Meier Cumulative Risk of the Primary Outcome, Stratified According to GRACE Risk Score at Baseline.

Patients who had a risk score of more than 140 on the Global Registry of Acute Coronary Events (GRACE) scale (high risk) benefited more from early intervention than did patients with a score of 140 or less (low-to-intermediate risk) with respect to the composite primary outcome of death, myocardial infarction, or stroke.

egy was not superior to a delayed-intervention strategy for the prevention of death, myocardial infarction, or stroke. However, an early-intervention strategy significantly reduced the secondary outcome of death, myocardial infarction, or refractory ischemia and appeared to be superior among high-risk patients for both the primary outcome and one of the secondary outcomes. There was no evidence of hazard associated with early intervention, and there were no differences in major bleeding or stroke between the two groups.

Although meta-analyses of previous randomized trials that compared an invasive strategy with a conservative strategy in patients with acute coronary syndromes have shown a benefit for an invasive strategy,^{2,3} the timing of angiography in the invasive-strategy group of these previous studies ranged from as early as 19 hours after randomization in one large trial¹² to as late as 96 hours in another large trial.⁸ Given this wide variation in the timing, there remains substantial uncertainty regarding the optimal timing for intervention in such patients.² Small, randomized trials comparing early intervention with delayed intervention have generated conflicting results.^{11,13} Although some observational analyses have suggested that earlier intervention, as compared with delayed intervention, may reduce events,^{17,18} others have suggested that outcomes appear to be similar between the two approaches.¹⁹ Also, there

has been a suggestion of a hazard associated with routine early intervention.^{2,8,12,20}

The lack of a significant difference in the rate of death, myocardial infarction, or stroke in the overall population between these two invasive strategies suggests that most patients with acute coronary syndromes can be treated safely with either early intervention or delayed intervention. It is noteworthy that the median time to angiography in the early-intervention group was 14 hours, which is significantly earlier than the median time to angiography in the previous large trials of invasive versus conservative management.^{7-9,12,20-22} In exploratory analyses, we found no evidence of heterogeneity in outcomes among study centers where angiography was performed within 6 hours, from 6 to 12 hours, or after 12 hours in the early-intervention group, suggesting that very early intervention (i.e., within 6 hours) is unlikely to provide significant additional benefit. However, the confidence intervals were wide in this analysis, and we cannot definitively rule this out as a possibility.

An additional benefit of early intervention was that it significantly reduced the risk of the composite of death, myocardial infarction, or refractory ischemia by more than one quarter. Refractory ischemia was associated with an increase by a factor of more than 4 in the risk of subsequent myocardial infarction, suggesting that refractory ischemia is a clinically important outcome. This, together with the lack of an early hazard and similar bleeding rates in the two groups, suggests that routine early intervention may be a preferred option for patients with acute coronary syndromes when access to cardiac catheterization and PCI capability is readily available. When access to these facilities is not readily available (e.g., on weekends or after hours), the results of our study provide reassurance that patients who are not at high risk can undergo interventions less urgently.

Some reports have suggested that an invasive strategy, as compared with a selectively invasive (or conservative) strategy, may increase the risk of events in women with acute coronary syndromes.^{23,24} We did not study a conservative-therapy group, so our results cannot confirm or refute these data. However, we did show that the risk of events with early intervention, as compared with delayed intervention, was consistent in women and men. Thus, if an invasive strategy

is selected for women with acute coronary syndromes, there does not appear to be harm if the intervention is performed early.

A potentially important finding in our study was that in high-risk patients (approximately one third of the study population, according to GRACE scores¹⁶), early intervention appeared to provide a significant benefit in the prevention of death, myocardial infarction, or stroke. In patients at low-to-intermediate risk (approximately two thirds of all patients), outcomes between the two strategies appeared to be almost identical. Although caution is required in evaluating subgroups when the primary outcome is not statistically significant, our findings are consistent with the results of previous intervention trials⁷⁻⁹ and are clinically and biologically plausible. Moreover, this observation builds on current guidelines for patients with acute coronary syndromes that recommend risk stratification for all such patients.²⁵⁻²⁷ The guidelines also suggest that in high-risk patients, intervention within 24 hours is superior to a strategy of delaying intervention to more than 36 hours. For all other patients with acute coronary syndromes, either an early or a delayed approach is safe and acceptable.

A limitation of our study was that even with a sample size of more than 3000 patients, the trial may have been relatively underpowered. A strength of the trial was that since the primary outcome focused on hard clinical outcomes, our results offer important information for the practicing clinician regarding the appropriate timing of intervention in patients with acute coronary syndromes.

In summary, our study showed that in most patients with acute coronary syndromes without

ST-segment elevation, an early-intervention strategy did not differ from a delayed-intervention strategy in preventing a composite outcome of death, myocardial infarction, or stroke. However, early intervention significantly reduced the risk of refractory ischemia and appeared to be superior to a delayed strategy in high-risk patients.

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APPENDIX

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