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ORIGINAL RESEARCH

Importance of Risk Assessment in Timing of Invasive Coronary Evaluation and Treatment of Patients With Non–ST-Segment–Elevation Acute Coronary Syndrome: Insights From the VERDICT Trial

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BACKGROUND: The optimal timing of invasive examination and treatment of high-risk patients with non–ST-segment–elevation acute coronary syndrome has not been established. We investigated the efficacy of early invasive coronary angiography compared with standard-care invasive coronary angiography on the risk of all-cause mortality according to the GRACE (Global Registry of Acute Coronary Events) risk score in a predefined subgroup analysis of the VERDICT (Very Early Versus Deferred Invasive Evaluation Using Computerized Tomography) trial.

METHODS AND RESULTS: Patients with clinical suspicion of non–ST-segment–elevation acute coronary syndrome with ECG changes indicating new ischemia and/or elevated troponin, in whom invasive coronary angiography was clinically indicated and deemed logistically feasible within 12 hours, were eligible for inclusion. Patients were randomized 1:1 to an early (≤12 hours) or standard (48–72 hours) invasive strategy. The primary outcome of the present study was all-cause mortality. Of 2147 patients randomized in the VERDICT trial, 2092 patients had an available GRACE risk score. Of these, 1021 (48.8%) patients had a GRACE score >140. During a median follow-up of 4.1 years, 192 (18.8%) and 54 (5.0%) patients died in the high and low GRACE score groups, respectively. The risk of death with the early invasive strategy was increased in patients with a GRACE score ≤140 (hazard ratio [HR], 2.04 [95% CI, 1.16–3.59]), whereas there was a trend toward a decreased risk of death with the early invasive strategy in patients with a GRACE score >140 (HR, 0.83 [95% CI, 0.63–1.10]) ($P_{interaction}$=0.006).

CONCLUSIONS: In patients with non–ST-segment–elevation acute coronary syndrome, we found a significant interaction between timing of invasive coronary angiography and GRACE score on the risk of death. Randomized clinical trials are warranted to establish the efficacy and safety among high-risk and low-risk patients with non–ST-segment–elevation acute coronary syndrome.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifier: NCT02061891.

Key Words: acute coronary syndrome ■ GRACE score ■ heart failure ■ invasive coronary angiography ■ mortality

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CLINICAL PERSPECTIVE

What Is New?

- In this predefined subgroup analysis of the VERDICT (Very Early Versus Deferred Invasive Evaluation Using Computerized Tomography) trial, there was a significant interaction between timing of invasive coronary evaluation in patients with non–ST-segment–elevation acute coronary syndrome and GRACE (Global Registry of Acute Coronary Events) score on the risk of the death, with a trend toward a decreased risk with an early invasive strategy in patients with a GRACE score >140 and an increased risk with an early invasive strategy in patients with a GRACE score ≤140.
- An early invasive strategy reduced the risk of all-cause mortality in patients with ECG changes, higher heart rate, and lower systolic blood pressure.

What Are the Clinical Implications?

- Given the exploratory nature of this study, large-scale randomized clinical trials, preferably with long-term follow-up, are warranted to establish not only whether an early invasive strategy is beneficial in high-risk patients with non–ST-segment–elevation acute coronary syndrome, but also whether an early invasive strategy can be harmful among those with a low risk.

Nonstandard Abbreviations and Acronyms

GRACE	Global Registry of Acute Coronary Events
ICA	invasive coronary angiography
TIMACS	Timing of Intervention in Acute Coronary Syndromes trial
VERDICT	Very Early Versus Deferred Invasive Evaluation Using Computerized Tomography trial

During the past decades, advances in the management of patients with non–ST-segment–elevation acute coronary syndrome (NSTE-ACS) have led to significant improvements in prognosis and life expectancy.[1–4] The optimal timing of invasive coronary angiography (ICA) and revascularization in NSTE-ACS, however, remains a challenge.[5,6] Although several randomized trials have failed to show any overall benefit of an early invasive strategy on short-term clinical outcomes in patients with NSTE-ACS, there is some evidence of reduced short-term mortality among high-risk patients.[7–14] Consequently, current guidelines recommend an early invasive strategy within 24 hours of hospital admission in patients with NSTE-ACS and a high-risk profile, including those with a GRACE (Global Registry of Acute Coronary Events) risk score >140.[5,6] Because the recommendation to perform early ICA can be logistically demanding for many health care systems, it appears important to investigate the efficacy of early invasive coronary evaluation on long-term mortality in high-risk populations.

In the VERDICT (Very Early Versus Deferred Invasive Evaluation Using Computerized Tomography) trial, a strategy of early invasive coronary evaluation and treatment did not reduce the risk of a composite of all-cause mortality, nonfatal acute myocardial infarction, or hospital admission for refractory myocardial ischemia or heart failure in patients with NSTE-ACS, except for those with a GRACE risk score >140.[15] Accordingly, we performed a predefined subgroup analysis of the VERDICT trial to determine the efficacy of early invasive therapy compared with a standard-care invasive examination and therapy on all-cause mortality and other clinical outcomes according to the GRACE risk score overall and according to its components.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

The VERDICT trial was a multicenter, open-label, parallel-group, randomized controlled trial, evaluating the optimal timing of ICA in patients with NSTE-ACS. Patients were randomized 1:1 to have a coronary angiography performed within 12 hours from time of diagnosis or a standard-care ICA within 48 to 72 hours.[15] The trial was conducted as a pragmatic clinical study embedded in routine clinical practice at the participating hospitals. The study was approved by the Danish National Committee on Health Research Ethics (approval number H-4-2010-039) and the Danish Data Protection Agency, and all patients gave written informed consent. The corresponding author has had full access to all data of the study and takes responsibility for its integrity and the data analysis.

Study Patients

Patients from 9 hospitals in the Capital Region of Copenhagen in Denmark aged ≥18 years admitted with chest pain and clinical suspicion of acute coronary syndrome were eligible for inclusion, whenever ICA was deemed clinically indicated and logistically possible within 12 hours from time of diagnosis provided one of the following criteria were fulfilled: (1) ECG changes indicating new ischemia (new ST-segment depression, horizontal or down sloping ≥0.05 mV in 2

consecutive leads, or T-wave inversion >0.01 mV in 2 leads with prominent R wave or R/S ratio >1) and/or (2) an increase in cardiac biomarkers of ischemia (plasma troponin). Because the trial was conducted as a pragmatic clinical study, plasma troponin was measured with contemporary clinical routine assays at the local laboratories of the participating hospitals. Exclusion criteria were pregnancy, patient inability to understand trial information, an indication for acute ICA (high-risk NSTE-ACS), expected survival <1 year, and known intolerance to platelet inhibitors, heparin, or contrast that could not be remedied medically.[15]

Study Procedures

At time of hospitalization and before randomization, patients received oral β-blockers, statins, anticoagulants, and antiplatelet therapy according to guidelines, unless contraindicated.[15] After the provision of informed consent, patients were randomized to an early or a standard invasive treatment strategy, and randomization was stratified by including site. Patients randomized to the early invasive strategy were transferred immediately from the referring hospital to the invasive center for ICA and possible revascularization, except during the night, where patient transfer was postponed to the early morning. Patients randomized to a standard invasive strategy were transferred within 48 to 72 hours to the invasive center. ICA was performed according to guidelines and clinical practice at the individual invasive center, and procedural diagnostic methods, procedural medication, and coronary revascularization were performed at the discretion of the interventional cardiologist, as previously described.[15]

GRACE Score

The GRACE risk score models were developed for the assessment of short- and long-term risk of death in patients with acute coronary syndrome.[16,17] The total GRACE risk score is calculated by adding the points assigned to the following variables evaluated at hospital presentation: age, systolic blood pressure, heart rate, serum creatinine, cardiac arrest at admission, elevated cardiac biomarkers, ST-segment deviation, and Killip class at presentation. However, the weighting of these variables differs according to the model version. In the VERDICT trial, the original GRACE risk score for in-hospital mortality was calculated, as described previously.[16] Although data on the variables included in the GRACE risk score were collected prospectively, the GRACE risk score was calculated retrospectively. In the present study, patients were categorized in high- or low-risk groups according to scores >140 or ≤140, respectively.[5,6] We also examined the efficacy of early versus standard invasive strategy according to quartiles of the GRACE risk score.

Study Outcomes

In the VERDICT trial, the primary outcome was the composite of all-cause mortality, hospital admission for heart failure, nonfatal acute myocardial infarction, and hospital admission for refractory myocardial ischemia. The primary outcome of the present predefined subgroup analysis was all-cause mortality, and secondary outcomes were hospital admission for heart failure, nonfatal acute myocardial infarction, and hospital admission for refractory myocardial ischemia. Vital status (ie, whether a person is alive and a resident in Denmark, emigrated, or dead, along with the date of these events) was obtained from the Danish Civil Registration System.[18] All other outcomes were assessed by review of patients' electronic and hard copy medical files and adjudicated by an event committee blinded to treatment allocation.

In this predefined subgroup analysis, causes of death were also examined. Causes of death, classified according to the *International Classification of Diseases, Tenth Revision* (*ICD-10*), were obtained from the Danish Registry of Causes of Death and categorized as cardiovascular and noncardiovascular based on the underlying cause.[19] Cardiovascular death was further subcategorized into acute myocardial infarction, chronic ischemic heart disease/heart failure/cardiomyopathy, and other, and noncardiovascular death into cancer, bleeding, and other. Unknown cause of death was classified as cardiovascular death.

Statistical Analysis

Baseline and procedural characteristics were summarized as frequencies with percentages or medians with 25th to 75th percentiles, and differences were tested with the χ^2 or Fisher exact test for categorical variables and the Mann-Whitney test for continuous variables. The absolute risks of outcomes including all-cause mortality were estimated with the Kaplan-Meier estimator, and differences between groups according to the GRACE score were assessed using the log-rank test. The absolute risks of the other outcomes were estimated using the Aalen-Johansen estimator, taking the competing risk of death into account, and differences between treatment groups according to the GRACE score were assessed using the Gray test.[20] Cause-specific univariable Cox regression models were used to compare the rates of outcomes between treatment groups according to the GRACE score and presented as hazard ratio (HR) with 95% CI. The proportional hazards assumption was fulfilled for all outcomes. Statistical interactions between treatment assignment and the GRACE score on outcomes were tested for using the likelihood ratio test.

In addition, cause-specific univariable Cox regression models were used to compare the rate of the primary outcome between treatment groups according to the components of the GRACE score. Age, creatinine, heart rate, and systolic blood pressure were each divided into quartiles. All statistical analyses were performed with SAS statistical software (SAS 9.4; SAS Institute, Cary, N.C.).

RESULTS

A total of 2147 patients were randomized in the VERDICT trial. Of these, 55 (2.6%) patients were excluded in this analysis due to lack of data on the GRACE score (2.0% and 3.2% in the early invasive and standard invasive strategy group, respectively). Of the remaining 2092 patients, 1021 (48.8%) had a GRACE score >140 (49.1% and 48.6% in the early invasive and standard invasive strategy group, respectively). Baseline characteristics according to treatment assignment in patients with a high and low GRACE score were not significantly different (Table 1). Tables 2 and 3 display the procedural and angiographic findings and details of coronary revascularization according to treatment assignment and GRACE score group. The procedural, angiographic, and revascularization characteristics did not differ significantly between the 2 groups according to GRACE score except for a slightly higher proportion

Table 1. Baseline Clinical Characteristics According to GRACE Score

	GRACE ≤140			GRACE >140		
	Standard, n=534	Early, n=537	*P* value*	Standard, n=504	Early, n=517	*P* value*
Age, y, mean (SD)	56.1 (10.0)	56.4 (10.1)	0.54	71.2 (9.9)	71.0 (9.2)	0.45
Sex, n (%)	364 (68.2)	363 (67.6)	0.84	307 (60.9)	337 (65.2)	0.16
BMI, kg/m^2, mean (SD)	27.7 (5.0)	27.4 (5.0)	0.17	26.6 (4.6)	26.4 (4.3)	0.60
Smoking, n (%)			0.35			0.69
Prior smoker	190 (35.6)	174 (32.4)		203 (40.3)	221 (42.7)	
Current smoker	185 (36.4)	208 (38.7)		133 (26.4)	127 (24.6)	
Comorbidities history						
Diabetes, n (%)	76 (14.2)	69 (12.9)	0.51	92 (18.3)	85 (16.4)	0.44
Hypertension, n (%)	265 (49.6)	247 (46.0)	0.23	295 (58.5)	286 (55.3)	0.30
Obstructive pulmonary disease, n (%)	52 (9.7)	55 (10.2)	0.78	104 (20.6)	113 (21.9)	0.63
Renal disease, n (%)	32 (6.0)	23 (4.3)	0.21	63 (12.5)	67 (13.0)	0.83
Stroke, n (%)	32 (6.0)	32 (6.0)	0.98	47 (9.3)	59 (11.4)	0.27
Valve disease, n (%)	12 (2.3)	13 (2.4)	0.85	39 (7.7)	21 (4.1)	0.02
Heart failure, n (%)	34 (6.4)	36 (6.7)	0.82	67 (13.3)	70 (13.5)	0.91
Acute myocardial infarction, n (%)	86 (16.1)	77 (14.3)	0.52	95 (18.8)	105 (20.3)	0.56
Percutaneous coronary intervention, n (%)	75 (14.0)	77 (14.3)	0.89	83 (16.5)	71 (13.7)	0.22
Coronary artery bypass grafting, n (%)	14 (2.6)	15 (2.8)	0.86	41 (8.1)	40 (7.7)	0.81
GRACE score and components						
GRACE score, mean (SD)	116.4 (16.9)	117.7 (15.8)	0.29	166.6 (20.9)	165.5 (19.6)	0.62
Killip class, n (%)			0.41			0.50
1	529 (99.1)	529 (98.5)		467 (92.7)	481 (93.0)	
2	5 (0.9)	8 (1.5)		30 (5.9)	25 (4.8)	
3	0 (0.0)	0 (0.0)		7 (1.4)	11 (2.1)	
Creatinine, mg/dL, mean (SD)	74.2 (17.6)	74.7 (17.9)	0.51	79.3 (22.9)	80.5 (22.6)	0.37
Heart rate, bpm, mean (SD)	73.5 (15.5)	73.9 (15.2)	0.58	80.8 (20.9)	80.5 (21.0)	0.77
Systolic blood pressure, mm Hg, mean (SD)	142.9 (22.0)	142.3 (21.0)	0.55	138.6 (21.3)	138.0 (21.5)	0.76
ECG with new ischemia, n (%)	98 (18.4)	103 (19.2)	0.73	306 (60.7)	305 (59.0)	0.58
Elevated troponin, n (%)	373 (69.9)	396 (73.7)	0.16	444 (88.1)	447 (86.6)	0.43

BMI indicates body mass index; and GRACE, Global Registry of Acute Coronary Events.
*χ^2 or Wilcoxon test.

Table 2. Procedural and Coronary Angiographic Characteristics

	GRACE ≤140			GRACE >140		
	Standard, n=534	Early, n=537	*P* value*	Standard, n=504	Early, n=517	*P* value*
Coronary angiography, n (%)	512 (95.9)	527 (98.1)	0.03	464 (92.1)	494 (95.6)	0.02
Time from randomization to coronary angiography, h, median (IQR)†	61.8 (37.1–87.8)	4.2 (2.8–10.5)	<0.001	60.2 (40.0–85.1)	5.1 (3.3–13.3)	<0.001
Femoral access, n (%)†	441 (82.6)	468 (88.8)	0.19	391 (84.3)	412 (83.4)	0.72
Angiographic characteristics, n (%)†			0.81			0.22
No coronary stenosis	199 (38.9)	195 (37.0)		109 (23.5)	131 (26.5)	
Left main coronary artery stenosis	15 (2.9)	19 (3.6)		39 (8.4)	51 (10.3)	
1-V_D	190 (37.1)	191 (36.2)		143 (30.8)	155 (31.4)	
2-V_D	69 (13.5)	83 (15.7)		83 (17.9)	887 (17.6)	
3-V_D	39 (7.6)	39 (7.4)		90 (19.4)	70 (14.2)	
≥1 occluded coronary artery, n (%)†	92 (18.0)	118 (22.4)	0.08	145 (31.3)	153 (31.0)	0.93
Left anterior descending artery stenosis, n (%)†	182 (35.5)	205 (38.9)	0.26	261 (56.3)	259 (52.4)	0.24
Left circumflex artery stenosis, n (%)†	143 (27.9)	147 (27.9)	1.00	180 (38.8)	187 (37.9)	0.77
Right coronary artery stenosis, n (%)†	149 (29.1)	165 (31.3)	0.44	215 (46.3)	201 (40.7)	0.08

GRACE indicates Global Registry of Acute Coronary Events; IQR, interquartile range; and V_D, vessel disease.
*χ^2 test, Fisher exact test, or Wilcoxon test.
†The denominators are the number of patients who underwent coronary angiography.

of patients in the early invasive group who underwent coronary angiography. Likewise, invasive procedural complications and antithrombotic therapy at discharge did not differ significantly between the early and standard treatment groups according to the GRACE score (Tables S1 and S2).

Table 3. Details of Coronary Revascularization Procedures

	GRACE <140			GRACE >140		
	Standard, n=534	Early, n=537	*P* value*	Standard, n=504	Early, n=517	*P* value*
PCI performed, n (%)	221 (41.4)	253 (47.1)	0.06	208 (41.3)	233 (45.1)	0.22
>1 drug-eluting stent, n (%)†	195 (88.2)	217 (85.8)	0.43	177 (85.1)	196 (84.1)	0.78
>1 bare-metal stent, n (%)†	7 (3.2)	8 (3.2)	1.00	12 (5.8)	20 (8.6)	0.26
Balloon angioplasty alone, n (%)†	11 (5.0)	18 (7.1)	0.33	16 (7.7)	17 (7.3)	0.87
Staged PCI, n (%)	3 (0.6)	3 (0.6)	1.00	5 (1.0)	3 (0.6)	0.50
Complete revascularization by PCI, n (%)†	184 (83.3)	207 (81.8)	0.71	154 (74.0)	167 (71.7)	0.58
No. of treated lesions, n (%)†			0.66			0.26
1	175 (79.2)	203 (80.2)		171 (82.2)	173 (74.2)	
2	40 (18.1)	38 (15.0)		27 (13.0)	44 (18.9)	
3	5 (2.3)	10 (4.0)		8 (3.8)	11 (4.7)	
>4	1 (0.5)	1 (0.4)		1 (0.5)	4 (1.7)	
No. of stents, n (%)†			0.20			0.26
0	15 (6.8)	30 (11.9)		20 (9.6)	16 (6.9)	
1	143 (64.7)	152 (60.1)		136 (65.4)	140 (60.1)	
2	54 (24.4)	56 (22.1)		36 (17.3)	52 (22.3)	
>3	9 (4.1)	15 (5.9)		16 (7.7)	25 (10.7)	
CABG, n (%)	50 (9.4)	53 (9.9)	0.78	78 (15.5)	76 (14.7)	0.73

CABG indicates coronary artery bypass grafting; GRACE, Global Registry of Acute Coronary Events; and PCI, percutaneous coronary intervention.
*χ^2 or Fisher exact test.
†The denominators are the number of patients who underwent PCI.

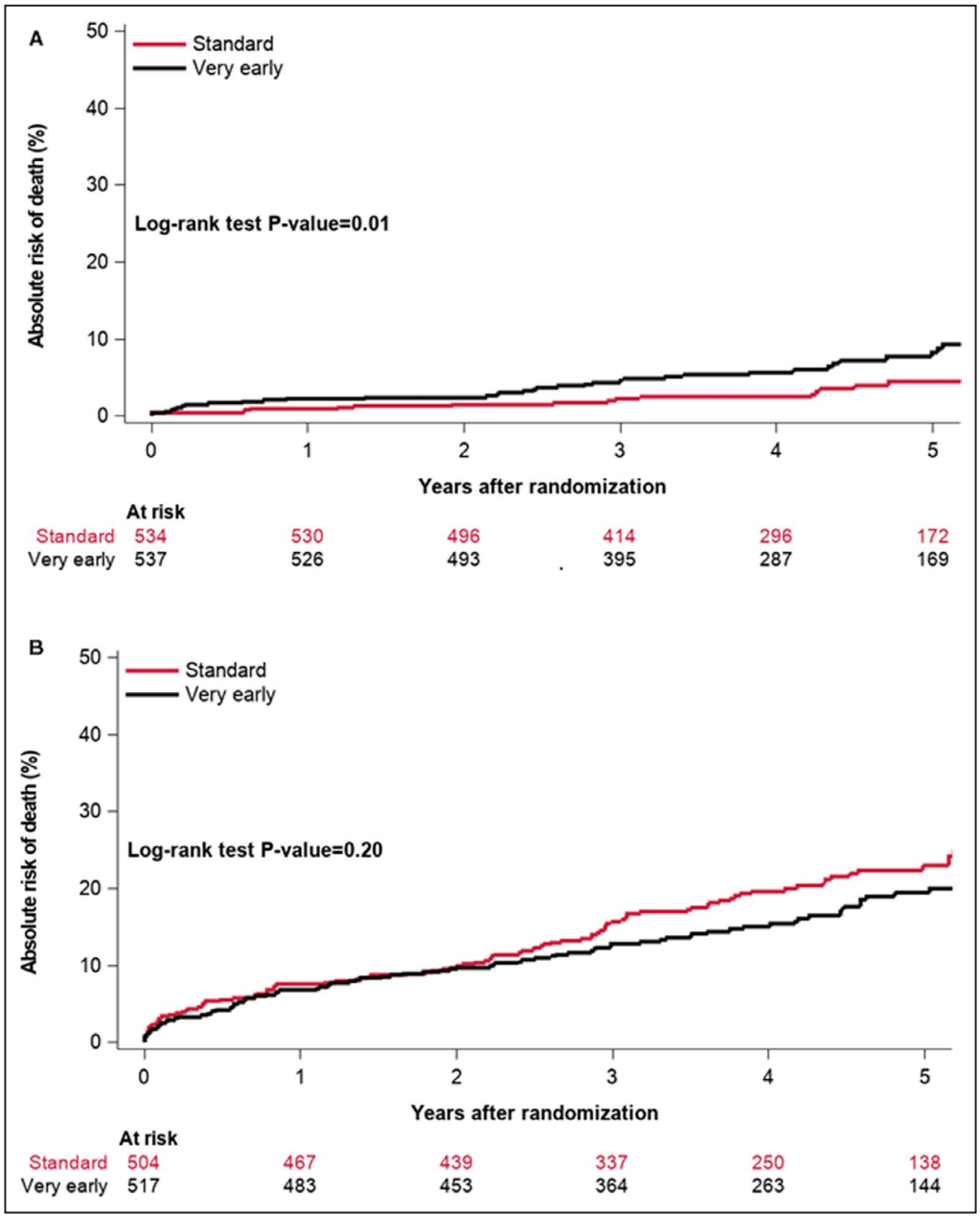

Figure 1. Absolute risk of death according to GRACE score (above/below median).
A, GRACE score <140. **B**, GRACE score >140. GRACE indicates Global Registry of Acute Coronary Events.

Primary Outcome

The median follow-up time of the study population was 4.1 years (25th–75th percentile, 2.9–5.3 years). The absolute risk of the all-cause mortality is displayed in Figure 1A and 1B. There was a significant interaction between treatment assignment and GRACE score on the risk of the death. Although there was a trend toward a decreased risk of all-cause mortality with the early invasive strategy in patients with a GRACE score >140 (HR, 0.83 [95% CI, 0.63–1.10]), the risk of all-cause mortality with an early invasive strategy was increased in patients with a GRACE score ≤140 (HR, 2.04 [95% CI, 1.16–3.59]) (*P* for interaction = 0.006).

Table 4 shows the distribution of specific causes of death according to treatment groups in patients with a high and low GRACE score. In patients with a GRACE score ≤140, the proportion of deaths attributed to a cardiovascular cause was higher in the early invasive group compared with the standard invasive group.

Secondary Outcomes

The absolute risks of heart failure hospitalization according to treatment assignment in patients with high

Table 4. Causes of Death

	GRACE <140		GRACE >140	
	Standard, n=18	Early, n=36	Standard, n=103	Early, n=89
Cardiovascular death, n (%)	7 (38.9)	21 (58.3)	54 (52.4)	42 (47.2)
Acute myocardial infarction	1 (5.6)	3 (8.3)	15 (14.6)	10 (11.2)
Ischemic heart disease/heart failure/cardiomyopathy	3 (16.7)	7 (19.4)	22 (21.4)	18 (20.2)
Other	2 (11.1)	4 (11.1)	13 (12.6)	8 (9.0)
Unknown	1 (5.6)	7 (19.4)	4 (3.9)	6 (6.7)
Noncardiovascular death, n (%)	11 (61.1)	15 (41.7)	49 (47.6)	47 (52.8)
Cancer	4 (22.2)	11 (30.6)	21 (20.4)	18 (20.2)
Bleeding	2 (11.1)	1 (2.8)	2 (1.9)	2 (2.3)
Other	5 (27.8)	3 (8.3)	26 (25.2)	27 (30.3)

GRACE indicates Global Registry of Acute Coronary Events.

and low GRACE scores are displayed in Figure 2. HRs for the early versus standard invasive strategy on secondary outcomes according to GRACE score are shown in Figure 3. There was a significant interaction between treatment assignment and GRACE score on the risk of heart failure hospitalization; the early invasive strategy significantly reduced the risk of heart failure hospitalization in patients with a GRACE score >140, but not in those with a GRACE score ≤140 (*P* for interaction = 0.02). With respect to the risk of nonfatal acute myocardial infarction, refractory myocardial ischemia, and repeat coronary revascularization, there was no significant difference between the early and standard invasive strategy, irrespective of GRACE score group (*P* for interaction ≥0.21).

We also examined the efficacy of early versus standard invasive strategy according to quartiles of the GRACE risk score. Overall, this analysis confirmed the associations found in the main analyses (Table S3).

Subgroup Analyses of the Components of the GRACE Score

HRs for an early versus a standard invasive strategy on all-cause mortality according to the components of the GRACE score are shown in Figure 4. There was a significant interaction between treatment assignment and new signs of myocardial ischemia on ECG on the risk of the primary outcome, with a decreased risk in patients treated early (*P* for interaction = 0.01). A similar trend was observed in patients with a high heart rate (*P* for interaction = 0.01) and low systolic blood pressure (*P* for interaction = 0.07).

DISCUSSION

In this predefined subgroup analysis of the VERDICT trial, there was a significant interaction between timing of invasive coronary evaluation and GRACE score on the risk of the death. Specifically, we found a trend toward a decreased risk of all-cause mortality with an early invasive strategy in patients with a GRACE score >140, whereas the risk of all-cause mortality with an early invasive strategy was increased in patients with a GRACE score ≤140. There was also a significant interaction between timing of invasive coronary evaluation and GRACE score on the risk of heart failure hospitalization; the early invasive strategy significantly reduced the risk of heart failure hospitalization in patients with a GRACE score >140, but not in those with a GRACE score ≤140. In addition, an early invasive strategy reduced the risk of all-cause mortality in patients with ECG changes, higher heart rate, and lower systolic blood pressure.

Although the efficacy of immediate coronary revascularization by percutaneous coronary intervention in ST-segment–elevation myocardial infarction is well established,[21,22] the optimal timing of ICA and revascularization is less clear in NSTE-ACS.[5,6] It is possible that salvage of ischemic, jeopardized myocardium by prompt coronary revascularization may prevent the development of new-onset or worsening of established heart failure and thus improve survival in NSTE-ACS.[15,21,23] On the other hand, a longer period of pharmacotherapy with antiplatelet and lipid-lowering agents may stabilize culprit coronary plaque ruptures and optimize conditions for subsequent revascularization and thereby improve outcomes in NSTE-ACS.[15,23] Several randomized clinical trials and meta-analyses have failed to demonstrate any convincing beneficial effect of an early invasive strategy on outcomes in patients with NSTE-ACS overall.[7–14] Patients with NSTE-ACS represent a clinically heterogenous population, and it is likely that patients demonstrating higher risk features may benefit more from earlier intervention. In a prespecified subgroup analysis of the TIMACS

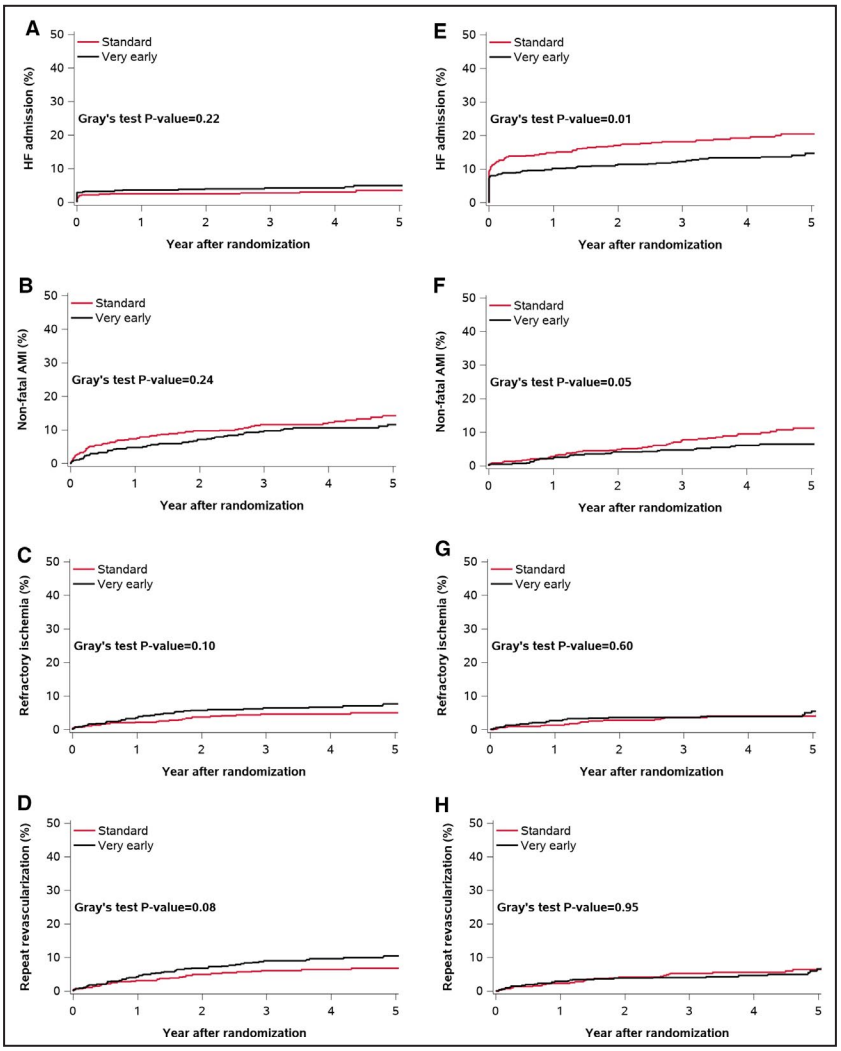

Figure 2. Absolute risk of secondary outcomes according to GRACE score (above/below median).
A, Heart failure hospitalization: GRACE score <140. **B**, Heart failure hospitalization: GRACE score >140. **C**, Nonfatal acute myocardial infarction: GRACE score <140. **D**, Nonfatal acute myocardial infarction: GRACE score >140. **E**, Refractory myocardial ischemia: GRACE score <140. **F**, Refractory myocardial ischemia: GRACE score >140. **G**, Repeat coronary revascularization: GRACE score <140. **H**, Repeat coronary revascularization: GRACE score >140. GRACE indicates Global Registry of Acute Coronary Events.

(Timing of Intervention in Acute Coronary Syndromes) trial, early coronary intervention reduced the risk of the composite of death, myocardial infarction, or stroke at 6 months, compared with standard coronary intervention in patients with a high (>140) GRACE score, whereas those with lower GRACE scores derived no benefit.[10] In a meta-analysis of 8 randomized controlled trials comparing early versus delayed invasive strategy in patients with NSTE-ACS, an early invasive strategy only reduced mortality in patients with a high (>140) GRACE score, but interaction between timing of invasive evaluation and GRACE score on the risk of death was not statistically significant.[14] In addition, there were substantial differences between trials included in this meta-analysis with respect to sample size and timing of invasive strategies, and the duration of follow-up was short.[14]

In our predefined subgroup analysis of the VERDICT trial, the effect of an early invasive strategy on all-cause mortality appeared to be modified by the GRACE risk score, and quantitatively opposite associations with GRACE score were suggested by our observations for heart failure hospitalization. A GRACE score >140 was also reported to be a significant predictor of high-risk coronary artery disease.[24] Given the higher prevalence of significant coronary artery disease in patients with a

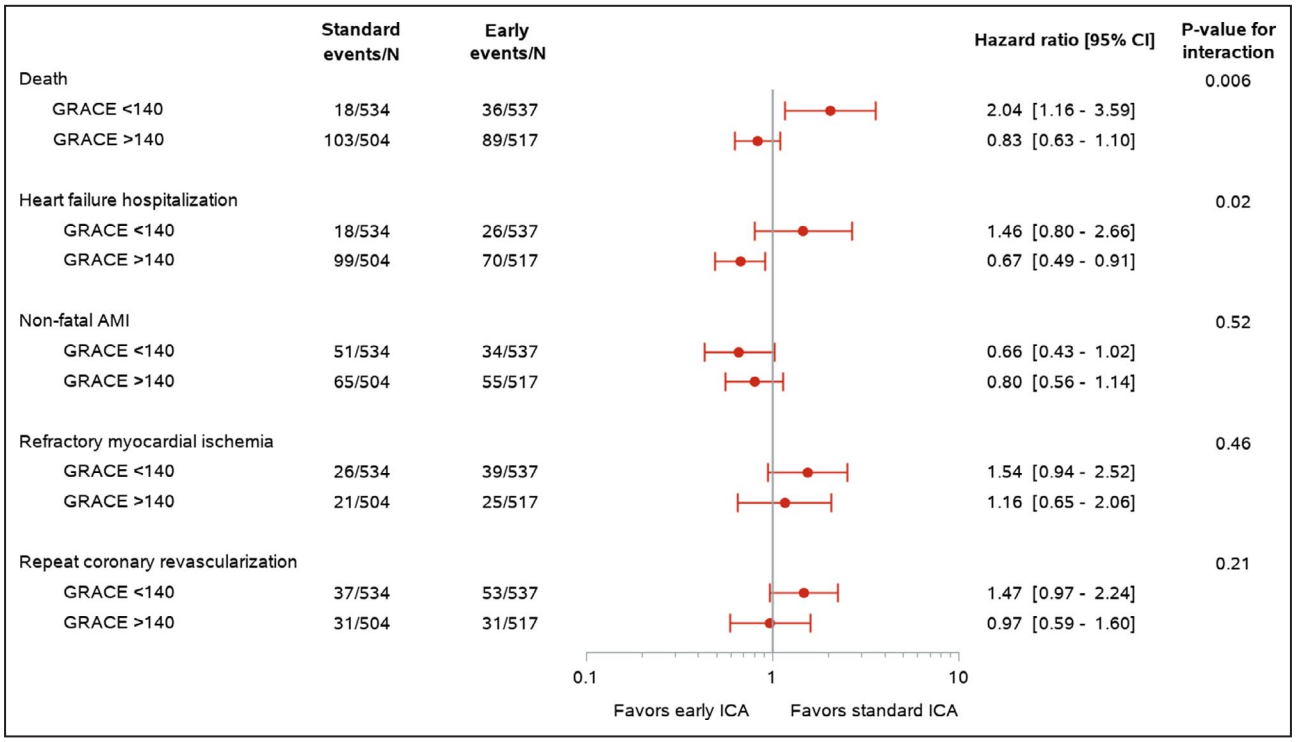

Figure 3. Treatment effect on outcomes according to GRACE score (above/below median).
AMI indicates acute myocardial infarction; GRACE, Global Registry of Acute Coronary Events; and ICA, invasive coronary angiography.

GRACE score >140 compared with those with a lower score in the VERDICT cohort, it can be hypothesized that the observed reduction in the risk of hard clinical end points with an early invasive strategy in patients at particularly high risk may result from prompt revascularization of severe coronary artery disease. These data substantially expand our knowledge on the efficacy of an early invasive strategy on clinically important outcomes in high-risk patients with NSTE-ACS and provide further support for the current guideline recommendations on the timing of invasive coronary evaluation in this subset of patients.[5,6] On the other hand, our data suggest a potential harm of an early invasive strategy among low-risk patients with NSTE-ACS. Although the present study does not provide a mechanistic basis for this finding, there may be several potential explanations. A beneficial effect of prolonged preprocedural pharmacotherapy with antiplatelet and lipid-lowering agents appears likely and may theoretically be superseded by early revascularization of high-risk coronary lesions in patients with a high GRACE score. The potential harm of an early strategy in low-risk patients was not related to periprocedural complications, despite a trend toward a higher proportion of low-risk patients with NSTE-ACS undergoing percutaneous coronary intervention in the early invasive evaluation arm. However, the trend toward a higher risk of refractory myocardial ischemia and repeat coronary revascularization, and a higher proportion of deaths attributed to a cardiovascular cause with the early invasive strategy in low-risk patients, raises concern for possible late adverse events including an excess mortality in this group. It also cannot be ruled out that the excess mortality observed in low-risk patients in the early ICA group, at least in part, may be attributed to a higher risk of stent thrombosis due to a more aggressive invasive treatment, although this explanation is speculative and appears to be less likely (especially given the lower risk of recurrent myocardial infarction with the early invasive strategy in low-risk patients).[25] On the other hand, the number of deaths in patients with low GRACE scores was low, making it difficult to draw definitive conclusions about the association between increased mortality and an early invasive strategy in these patients and the possibility of a chance finding more likely. Taken together, our findings raise the question whether the effect of an early invasive coronary evaluation in patients with NSTE-ACS may differ according to their GRACE risk score. However, it is important to emphasize that subgroup analyses should always be interpreted with caution given that clinical trials are not necessarily powered to answer these specific questions. There is also a potential risk of loss of randomization, and significant interactions may be spurious due to multiple testing. Thus, given the exploratory and hypothesis-generating nature of our study, large-scale randomized

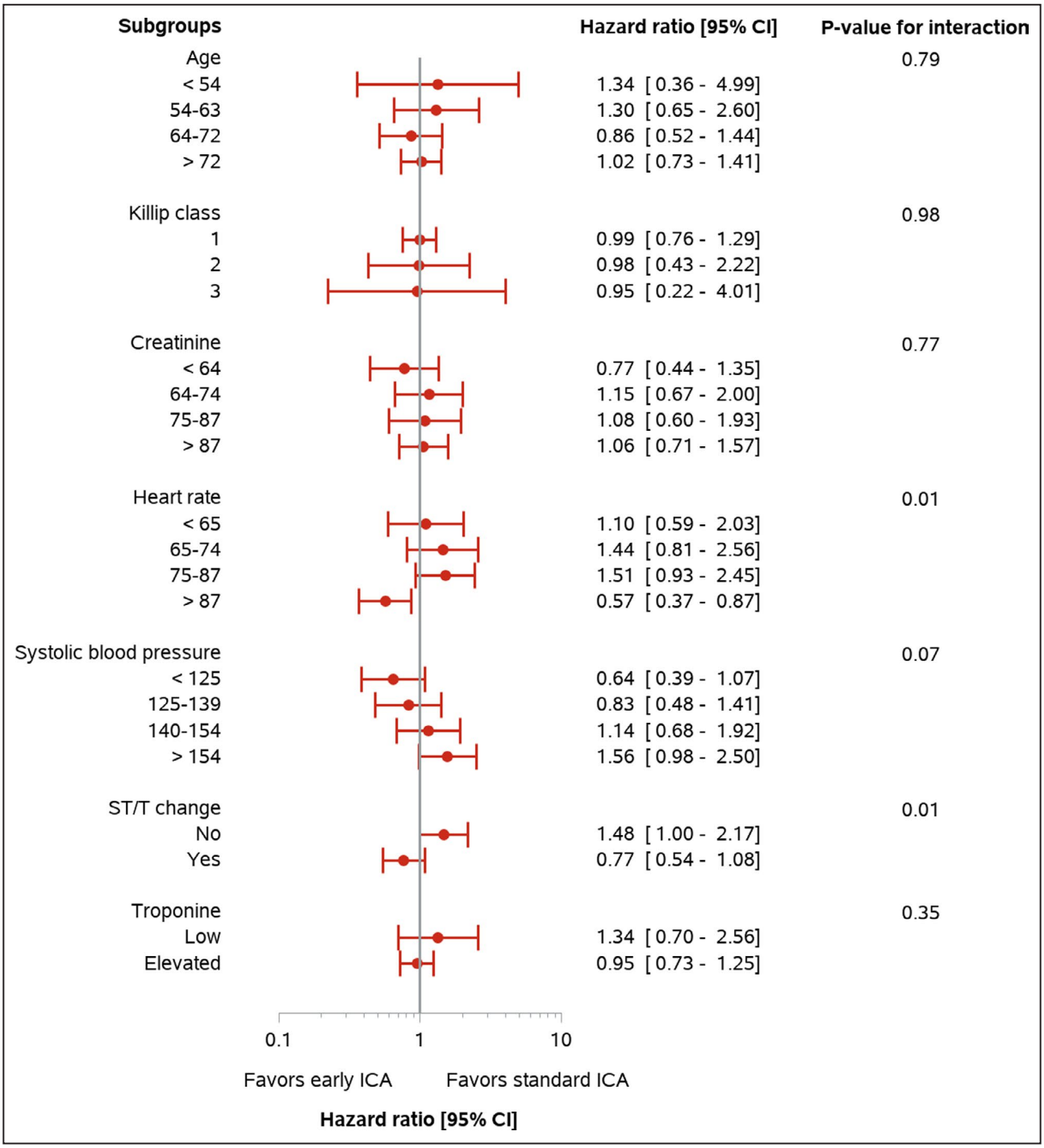

Figure 4. Treatment effect on the primary outcome of death according to the components of the GRACE score.
Units for creatinine are milligrams per deciliter. Units for systolic blood pressure are millimeters of mercury. GRACE indicates Global Registry of Acute Coronary Events; and ICA, invasive coronary angiography.

clinical trials with long-term follow-up are warranted to establish not only whether an early invasive strategy is beneficial in high-risk patients with NSTE-ACS, but also whether an early invasive strategy can be harmful among those with a low risk.

Although this subgroup analysis of the VERDICT trial further strengthens the utility of the GRACE score for risk stratification in NSTE-ACS, the significance of the individual components of the GRACE risk score on the timing of invasive coronary evaluation has not been investigated thoroughly. This study demonstrated that an early invasive strategy, as compared with a standard invasive strategy, reduced the risk of all-cause mortality and the development of heart failure in patients

with NSTE-ACS with ECG changes, but not in those without such changes. Although this is in contrast with the neutral results of the TIMACS trial and those on the primary composite end point in the VERDICT trial,[10,15] the finding supports the current guideline recommendations of early invasive coronary evaluation in patients with NSTE-ACS with ECG changes indicating ongoing myocardial ischemia.[5,6] Our study also demonstrated a trend toward a decreased risk of all-cause mortality with an early invasive strategy in patients with higher heart rate and lower systolic blood pressure, respectively. The beneficial effect of an early invasive strategy in these patients may suggest a stabilizing effect on vulnerable plaques that cause hemodynamic instability.

In contrast to previous findings, the early invasive strategy did not reduce the risk of refractory myocardial ischemia and repeat coronary revascularization in our patients. The reasons for these findings are not clear, but timing of invasive coronary evaluation could be of minor importance with respect to the risk of subsequent refractory myocardial ischemia and repeat coronary revascularization, whereas the extent and completeness of index coronary revascularization may play a more significant role.[26,27] In agreement with this notion, a similar and a notably high proportion of patients underwent complete revascularization in both VERDICT trial treatment arms. Thus, it is unclear why the frequency of refractory myocardial ischemia and repeat coronary revascularization was higher in patients with a low GRACE score allocated to an early invasive examination and treatment. However, the low number of events and the lack of statistically significant interactions between treatment allocation and GRACE score on the risk of these secondary outcomes make it difficult to draw firm conclusions on this topic.

Limitations

The findings of this study should be viewed in the context of potential limitations. First, 55 patients were excluded from our analysis due to the lack of GRACE score data. On the other hand, the proportion of patients with a missing GRACE score was similar in the 2 groups. Second, both the present and the TIMACS trial used the original GRACE risk score for prediction of future death. Due to different weighting of variables, other GRACE risk models may provide other results. Third, although the GRACE risk score was a predefined subgroup analysis, the assessment of clinical outcomes by the GRACE score was done post hoc, and this study was not powered to determine potential differences in outcome due to the early invasive strategy according to the GRACE score. Fourth, the primary outcome in this post hoc analysis differed from that of the original VERDICT trial, in that this post hoc analysis only focused on hard clinically important end points. Fifth, causes of death were retrieved from the Danish Registry of Causes of Death and were not adjudicated by an event committee. Sixth, it would have been interesting to assess whether differences in occurrence of stent thrombosis and adherence to antithrombotic therapy could explain the associations between the early invasive and standard invasive strategy and outcomes according to the GRACE score. However, data on stent thrombosis and adherence to antithrombotic therapy during follow-up were not available. Finally, subgroup analyses can only be considered hypothesis generating as mentioned above.

CONCLUSIONS

In this predefined subgroup analysis of the VERDICT trial, there was a significant interaction between timing of invasive coronary evaluation and GRACE score on the risk of the death, with a trend toward a decreased risk with an early invasive strategy in patients with a GRACE score >140 and an increased risk with an early invasive strategy in patients with a GRACE score ≤140. In addition, an early invasive strategy reduced the risk of all-cause mortality in patients with ECG changes, higher heart rate, and lower systolic blood pressure. Given the exploratory nature of this study, large-scale randomized clinical trials, preferably with long-term follow-up, are warranted to establish not only whether an early invasive strategy is beneficial in high-risk patients with NSTE-ACS, but also whether an early invasive strategy can be harmful among those with a low risk.

ARTICLE INFORMATION

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Supplementary Material

Tables S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. Invasive procedural complications according to GRACE score (above/below median)

	GRACE ≤140			GRACE >140		
	Standard N=534	Early N=537	P-value*	Standard N=504	Early N=517	P-value*
Cardiac arrest	2 (0.4)	0 (0.0)	N/A	2 (0.4)	2 (0.4)	1.00
Bleeding	11 (2.1)	7 (1.3)	0.34	8 (1.6)	12 (2.3)	0.40
Stroke/TIA	1 (0.2)	0 (0.0)	N/A	3 (0.6)	6 (1.2)	0.51
Non-fatal AMI	1 (0.2)	0 (0.0)	N/A	4 (0.8)	1 (0.2)	0.21

**Chi-square or Fisher's exact test.*

AMI, acute myocardial infarction; GRACE, Global Registry of Acute Coronary Events; TIA, transient ischemic attack.

Table S2. Antithrombotic therapy at discharge according to quartiles of GRACE score

	GRACE ≤140			GRACE >140		
	Standard N=534	Early N=537	P-value*	Standard N=504	Early N=517	P-value*
Aspirin	450 (84.3)	435 (81.0)	0.16	418 (82.9)	426 (82.4)	0.82
ADP-receptor inhibitors	380 (71.2)	365 (68.0)	0.26	350 (69.4)	366 (70.8)	0.64
Clopidogrel	104 (19.5)	95 (17.7)	0.45	125 (24.8)	128 (24.8)	0.99
Ticagrelor	269 (50.4)	259 (48.2)	0.48	222 (44.0)	232 (44.9)	0.79
Prasugrel	11 (2.1)	12 (2.2)	0.84	6 (1.2)	10 (1.9)	0.34
Oral anticoagulants	19 (3.6)	20 (3.7)	0.88	48 (9.5)	58 (11.2)	0.37

ADP, adenosine diphosphate; GRACE, Global Registry of Acute Coronary Events.

Table S3. Treatment effect on outcomes according to quartiles of GRACE score

	Standard Events/N	Early Events/N	Hazard ratio (95% CI)	P-value for Interaction
Death				0.04
GRACE <120	7/284	14/265	2.21 (0.89-5.48)	
GRACE 120-140	11/250	22/272	1.86 (0.90-3.84)	
GRACE 141-160	32/248	22/259	0.66 (0.39-1.14)	
GRACE >160	71/256	67/258	0.91 (0.65-1.27)	
Heart failure hospitalization				0.14
GRACE <120	5/284	10/265	2.20 (0.75-6.45)	
GRACE 120-140	13/250	16/272	1.14 (0.55-2.37)	
GRACE 141-160	34/248	23/259	0.64 (0.38-1.09)	
GRACE >160	65/256	47/258	0.69 (0.48-1.01)	
Non-fatal AMI				0.62
GRACE <120	25/284	13/265	0.56 (0.29-1.10)	
GRACE 120-140	26/250	21/272	0.73 (0.41-1.29)	
GRACE 141-160	29/248	20/259	0.64 (0.36-1.14)	
GRACE >160	36/256	35/258	0.92 (0.58-1.47)	
Refractory myocardial ischemia				0.57
GRACE <120	15/284	19/265	1.40 (0.71-2.75)	
GRACE 120-140	11/250	20/272	1.72 (0.82-3.59)	
GRACE 141-160	10/248	16/259	1.57 (0.71-3.46)	
GRACE >160	11/256	9/258	0.78 (0.32-1.89)	
Repeat coronary revascularization				0.27
GRACE <120	20/284	26/265	1.45 (0.81-2.59)	
GRACE 120-140	17/250	27/272	1.50 (0.82-2.75)	
GRACE 141-160	15/248	21/259	1.37 (0.71-2.66)	
GRACE >160	16/256	10/258	0.60 (0.27-1.32)	

AMI, acute myocardial infarction; GRACE, Global Registry of Acute Coronary Events.