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Outcomes of Patients With Prior Coronary Artery Bypass Grafting and Acute Coronary Syndromes

Analysis From the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) Trial

Eugenia Nikolsky, MD, PhD,*† Brent T. McLaurin, MD,‡ David A. Cox, MD,§ Steven V. Manoukian, MD,‖ Ke Xu, PhD,† Roxana Mehran, MD,†¶ Gregg W. Stone, MD†#

Haifa, Israel; New York, New York; Anderson, South Carolina; Charlotte, North Carolina; and Nashville, Tennessee

Objectives This study sought to assess the contemporary outcomes of patients with prior coronary artery bypass graft (CABG) who present with moderate and high-risk acute coronary syndromes (ACS) and are treated with an early invasive strategy and contemporary antithrombin regimens.

Background The prognosis of patients with ACS and prior CABG in relation to triage strategy and contemporary antithrombotic regimens is unknown.

Methods In the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial, 2,475 of 13,764 patients (18.0%) with ACS managed with an early invasive strategy had previously undergone CABG. Their outcomes were examined according to treatment and randomized antithrombin regimen.

Results Prior CABG was associated with older age, more frequent comorbidities, higher Thrombolysis In Myocardial Infarction risk score, and lower left ventricular ejection fraction. Patients with versus without prior CABG were less likely to undergo (repeat) CABG and were more likely to be managed medically. At 1 year, patients with versus without prior CABG had higher rates of major adverse cardiac events (MACE) (22.5% vs. 15.2%, $p < 0.0001$) due to greater mortality (5.4% vs. 3.9%, $p < 0.0001$), myocardial infarction (10.0% vs. 6.8%, $p < 0.0001$), and unplanned revascularization (13.1% vs. 8.2%, $p < 0.0001$). History of CABG was an independent predictor of MACE. The 1-year MACE rates were not significantly different after randomization to bivalirudin versus heparin plus a glycoprotein IIb/IIIa inhibitor (odds ratio: 1.24, 95% confidence interval: 0.90 to 1.70).

Conclusions Despite the progress in the treatment of coronary artery disease, patients with prior CABG and ACS have a poor prognosis, substantially worse than for those without prior CABG. Whereas bivalirudin monotherapy was an acceptable treatment for these patients, it did not improve their prognoses. (J Am Coll Cardiol Intv 2012;5:919–26) © 2012 by the American College of Cardiology Foundation

From the *Department of Cardiology, Rambam Health Care Campus and the Technion—Israel Institute of Technology, Haifa, Israel; †Cardiovascular Research Foundation, New York, New York; ‡AnMed Health, Anderson, South Carolina; §Mid Carolina Cardiology, Charlotte, North Carolina; ‖Sarah Cannon Research Institute and Hospital Corporation of America, Nashville, Tennessee; ¶Mount Sinai Medical Center, New York, New York; and the #Columbia University Medical Center, New York, New York. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Coronary artery bypass graft (CABG) was broadly introduced in the 1970s, and since then has become one of the most common surgical procedures in the United States (1). However, despite successful revascularization and secondary prevention measures, progression of atherosclerosis after CABG occurs both in grafts and native coronary arteries, resulting in significant morbidity and mortality, especially in patients who present with acute coronary syndromes (ACS) (2,3). Currently, an early invasive strategy is recommended for management of such patients (4). Nonetheless, in previous studies, patients with prior CABG and ACS reportedly have poor prognoses, regardless of management strategy (5–7). The outcomes of patients with prior CABG and ACS have not recently been reported from a large-scale contemporary study, and the optimal antithrombotic regimens have not been identified. Therefore, we assessed the outcomes of patients with a history of CABG presenting with ACS and undergoing an early invasive approach from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial.

Abbreviations and Acronyms

ACS = acute coronary syndromes(s)

CABG = coronary artery bypass graft

GPI = glycoprotein IIb/IIIa inhibitor

MACE = major adverse cardiac event(s)

MI = myocardial infarction

PCI = percutaneous coronary intervention

TIMI = Thrombolysis In Myocardial Infarction

Methods

Study design. The inclusion and exclusion criteria and principal results of the ACUITY trial have been reported in detail elsewhere (8–10). In brief, patients >18 years of age with symptoms of unstable angina lasting ≥10 min within the preceding 24 h were eligible if 1 or more of the following criteria were met: new ST-segment depression or transient elevation ≥1 mm; troponin or creatine kinase-myocardial band elevation; known coronary artery disease; or all 4 other TIMI (Thrombolysis In Myocardial Infarction) unstable angina risk criteria were positive (8). Eligible patients were randomized to the open-label use of 1 of 3 antithrombin regimens started before angiography: heparin (either unfractionated or enoxaparin) plus a glycoprotein IIb/IIIa inhibitor (GPI); bivalirudin plus a GPI; or bivalirudin monotherapy.

After mandatory angiography was performed within 72 h of randomization, the patients were triaged according to management by percutaneous coronary intervention (PCI), CABG, or medical therapy. Aspirin and clopidogrel were administered as previously described (8–10). In patients undergoing PCI, the type of stent used was determined by the operator's discretion.

Information as to whether previous CABG was performed was collected by site investigators at the time of study enrollment.

Clinical endpoints. The primary endpoint in ACUITY was major adverse cardiac events (MACE) (which are death from any cause, myocardial infarction [MI], or unplanned revascularization for ischemia), non-CABG major bleeding, and net adverse clinical events (MACE or major bleeding) (8). A Clinical Events Committee blinded to treatment assignment adjudicated all 30-day and 1-year primary endpoint and bleeding events.

Statistical analysis. Categorical variables were compared with chi-square or Fisher exact tests. Continuous variables are presented as medians with interquartile ranges and were compared using the Kruskal-Wallis test. Thirty-day and 1-year outcomes are presented as Kaplan-Meier estimates and were compared using log-rank tests. Multivariable logistic regression was used to identify independent predictors of outcomes in the entire ACUITY population adjusting for age, sex, diabetic status, hypertension, current smoking, prior MI, prior PCI, prior CABG, baseline cardiac biomarker elevation, ST-segment deviation, baseline estimated creatinine clearance (Cockcroft-Gault equation), baseline anemia, left ventricular ejection fraction, antithrombotic regimen randomization, and triage to PCI versus (repeat) CABG versus medical management. A forward stepwise algorithm was used to select significant covariates from this list. In addition, separate models of clinical outcomes were specifically created for patients with prior CABG.

Results

Baseline clinical characteristics. Among the 13,819 patients with ACS, information regarding CABG history was available in 13,764 (99.6%), 2,475 of whom (18.0%) had previously undergone CABG. Patients with versus without prior CABG had a significantly higher risk profile, except for ST-segment changes and abnormal cardiac biomarkers, which were less frequent in prior CABG patients (Table 1). A similar proportion of ACS patients with and without prior CABG were triaged to revascularization with PCI. However, treatment with (repeat) CABG was much less common in patients with prior CABG.

Clinical outcomes. Patients with versus without prior CABG had significantly greater 30-day rates of MACE, driven mainly by more frequent MI (Fig. 1A). Rates of MACE in prior CABG patients remained higher at 1 year, due to higher rates of mortality, MI, and unplanned revascularization (Figs. 1B and 2) of both target and nontarget vessels (6.9% vs. 5.0%, $p = 0.0009$ and 5.6% vs. 4.1%, $p = 0.004$, respectively).

Patients with prior CABG and ACS had a particularly high rate (10.0%) of developing a new MI (apart from the presenting event) within 1 year. Of the 239 infarcts that occurred within 1 year, approximately one-half ($n = 118$) occurred during the index hospitalization mainly due to revascularize-

Table 1. Baseline Clinical Data, Randomization Assignment, and Triage Strategy in Patients With and Without History of CABG

	Prior CABG (n = 2,475)	No Prior CABG (n = 11,289)	p Value
Age, yrs	67 (58–74)	62 (53–71)	<0.0001
Male	77.8	68.2	<0.0001
Diabetes	37.3	26.1	<0.0001
Hypertension	82.1	63.7	<0.0001
Hyperlipidemia	80.6	52.0	<0.0001
Current smoker	18.1	31.5	<0.0001
Previous myocardial infarction	57.2	25.9	<0.0001
History of PCI	57.6	34.8	<0.0001
LVEF, %	52 (40–60)	57 (50–65)	<0.0001
Anemia	22.8	15.6	<0.0001
Chronic renal insufficiency	25.2	17.7	<0.0001
Cardiac biomarker elevation	44.3	62.7	<0.0001
ST-segment deviation ≥1 mm	29.7	36.1	<0.0001
TIMI risk score			
Low (0–2)	3.1	18.4	<0.0001
Intermediate (3–4)	44.2	56.8	<0.0001
High (5–7)	52.7	24.8	<0.0001
Randomization to antithrombotic medications			
Unfractionated heparin + GPI	33.9	33.2	0.53
Bivalirudin + GPI	32.5	33.5	0.32
Bivalirudin alone	33.7	33.3	0.72
Treatment strategy			
PCI	55.4	56.6	0.25
CABG	2.9	13.0	<0.0001
Medical management	41.7	30.4	<0.0001

Values are median (interquartile range) or percentages.

CABG = coronary artery bypass graft; GPI = glycoprotein IIb/IIIa inhibitor; LVEF = left ventricle ejection fraction; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

tion procedures, whereas the other half (n = 121) occurred during follow-up related to recurrent ischemia.

History of CABG was an independent predictor of 1-year MACE and its individual components, including mortality (hazard ratio [HR]: 1.33; 95% confidence interval [CI]: 1.03 to 1.71, p = 0.028), MI (HR: 1.67; 95% CI: 1.41 to 1.97, p < 0.0001), and unplanned revascularization (HR: 1.40; 95% CI: 1.21 to 1.62, p < 0.0001) (Table 2).

Outcomes in the prior CABG group according to treatment. Following angiography, the 2,475 patients with prior CABG were treated by PCI (n = 1,370; 55.4%), repeat CABG (n = 73; 2.9%), or medically (n = 1,032; 41.7%). Among those undergoing PCI, intervention was performed on native arteries in 852 (62.2%), on bypass grafts in 552 (40.3%), and on both in 34 (2.5%) patients. Among those undergoing repeat CABG, a median of 3.0 grafts were placed, with arterial graft(s) used in 40 patients (54.8%). Thirteen patients (17.8%) had concurrent surgical procedures, including valvular and/or other nonspecified intervention. Among 1,032 patients triaged to medical management, revascularization was declined due to the physician's or patient's preference in 405 (39.2%) and in 15 (1.4%), respectively, due to lesion anatomy considered amenable for revascularization in 261 (25.3%), due to absence of significant lesion in 152 (14.7%), and due to poor patient's condition in 7 (0.7%) patients. The reason for not performing a revascularization was not specified in 192 (18.6%) patients.

Prior CABG patients undergoing repeat CABG compared with PCI or medical therapy had significantly higher 30-day and 1-year rates of MI (both Q-wave and non–Q-wave) and mortality (Table 3). Prior CABG patients undergoing PCI compared with medical management had significantly higher 30-day and 1-year rates of MI, unplanned revascularization, and non–CABG-related major bleeding.

Clinical outcomes stratified by history of CABG and management strategy are presented in Table 4. Prior CABG patients treated by CABG or PCI, compared with patients

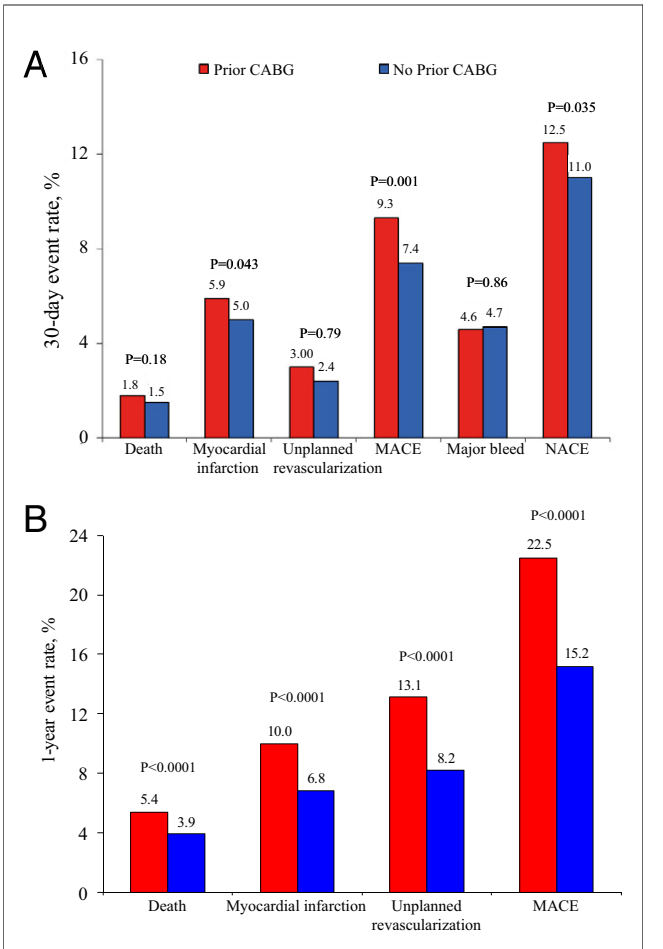

Figure 1. Outcomes of Patients With and Without Prior CABG at 30 Days and 1 Year

Outcomes of patients with and without prior coronary artery bypass graft (CABG) at 30 days **(A)** and 1 year **(B)**. MACE = major adverse cardiac event(s); NACE = net adverse clinical event(s).

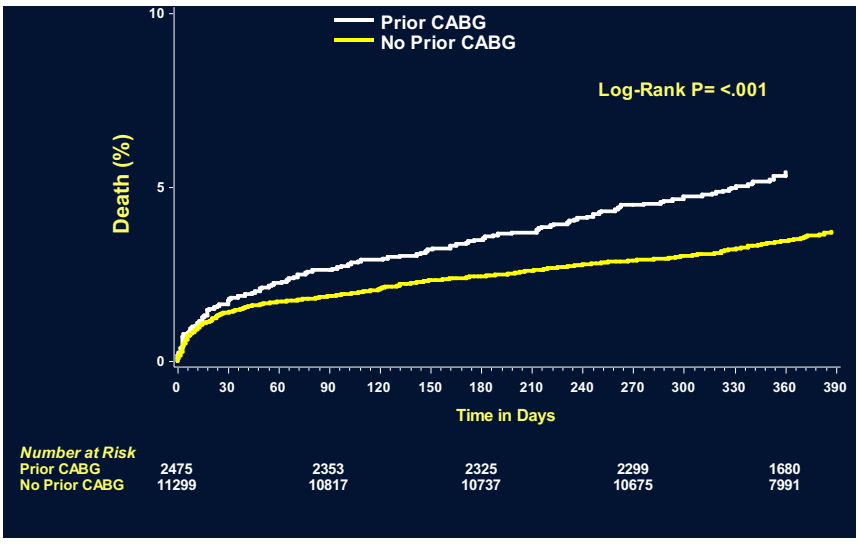

Figure 2. 1-Year Mortality in Patients With and Without Prior CABG

CABG = coronary artery bypass graft.

without prior CABG, had substantially higher rates of all adverse events except major bleeding. Repeat versus first CABG was also associated with more frequent CABG-related reoperations for bleeding (4.2% vs. 1.4%, p = 0.051) and blood product transfusions (58.8% vs. 40.4%, p = 0.003).

Among patients with prior CABG triaged to PCI, intervention on a graft compared with native vessel was associated with higher 30-day rates of MI (both Q-wave MI [2.1% vs. 0.8%, p = 0.04], non–Q-wave MI [9.4% vs. 5.4%, p = 0.008]), and MACE (14.8% vs. 9.2%, p = 0.002). At 1 year, MACE remained increased in patients after PCI of grafts (33.1% vs. 21.9%, p < 0.0001), due to higher rates of mortality (6.6% vs. 3.6%, p = 0.02), MI (Q-wave: 2.6% vs. 0.8%, p = 0.011; non–Q-wave: 16.2% vs. 7.8%, p < 0.0001), and unplanned revascularization (19.6% vs. 14.3%, p = 0.053).

The 1-year mortality was significantly higher among patients with prior CABG in whom the decision to be treated with medical management was made because of patient preference rather than physician guidance (20.6% vs. 5.4%, p = 0.018). The same was true for 1-year MACE (34.0% vs. 15.1%, p = 0.046).

Randomized antithrombotic therapy. The main baseline characteristics among patients with prior CABG were well matched among the 3 randomization arms (data not shown). The 30-day and 1-year outcomes according to randomization are presented in Figure 3. The multivariable predictors of 30-day and 1-year MACE in patients with prior CABG are shown in Figure 4. MACE at 30 days and 1 year were not significantly different after randomization to bivalirudin compared with heparin plus a GPI.

Table 2. Multivariate Predictors of 1-Year MACE in the Entire ACUITY Population

Variable	Logistic Coefficient	p Value	Hazard Ratio (95% CI)
Triage to CABG vs. medical therapy	0.96	<0.0001	2.61 (2.20, 3.10)
Triage to PCI vs. medical therapy	0.83	<0.0001	2.29 (2.02, 2.60)
History of CABG	0.41	<0.0001	1.51 (1.35, 1.70)
Baseline renal insufficiency	0.37	<0.0001	1.45 (1.30, 1.61)
History of PCI	0.28	<0.0001	1.32 (1.18, 1.48)
Baseline anemia	0.25	<0.0001	1.28 (1.14, 1.44)
Hypertension	0.18	0.0011	1.20 (1.07, 1.33)
ST-segment deviation ≥1 mm	0.18	0.0003	1.20 (1.09, 1.32)
Baseline cardiac biomarker elevation	0.17	0.0014	1.18 (1.07, 1.31)

ACUITY = Acute Catheterization and Urgent Intervention Triage Strategy; CI = confidence interval; MACE = major adverse cardiac event(s); other abbreviations as in Table 1.

Discussion

The main results of the present analysis are as follows. 1) Prior CABG is common in patients admitted for ACS. 2) Patients with prior CABG compared with those without previous surgical revascularization are at increased adjusted risk for ischemic events and 1-year mortality. 3) Bivalirudin monotherapy was an acceptable treatment for these patients, but did not improve their short-term or long-term prognosis. 4) In patients with prior CABG and ACS, revascularization with either PCI or repeat CABG was associated with high 30-day and 1-year rates of MI and repeat revascularization (especially with PCI of

Table 3. Clinical Outcomes of 2,475 Patients With Prior CABG and ACS Triaged to PCI, CABG, or Medical Management

Outcomes	PCI (n = 1,370)	Repeat CABG (n = 73)	Medical Management (n = 1,032)	P_1	P_2	P_3
At 30 days						
Death	1.4	12.4	1.7	<0.0001	0.60	0.0003
Myocardial infarction	8.7	21.2	1.3	0.0007	<0.0001	<0.0001
Q-wave	1.2	4.4	0.2	0.038	0.004	0.0005
Non–Q-wave	7.4	16.8	1.1	0.006	<0.0001	<0.0001
Unplanned revascularization	3.8	0.0	2.1	0.11	0.02	0.19
MACE	11.9	28.8	4.4	<0.0001	<0.0001	<0.0001
Non-CABG major bleeding	6.3	1.5	2.6	0.09	<0.0001	0.52
NACE	16.2	30.1	6.3	0.004	<0.0001	<0.0001
At 1 year						
Death	5.3	13.8	4.9	0.0006	0.64	0.0003
Myocardial infarction	13.5	21.2	4.6	0.038	<0.0001	<0.0001
Q-wave	1.6	4.4	0.6	0.08	0.03	0.0005
Non–Q-wave	12.1	16.8	4.1	0.14	<0.0001	<0.0001
Unplanned revascularization	17.3	12.1	7.7	0.30	<0.0001	0.19
MACE	27.8	39.2	14.3	0.007	<0.0001	<0.0001

Values are %.

ACS = acute coronary syndromes; NACE = net adverse clinical event(s); P_1 = PCI vs. repeat CABG; P_2 = PCI vs. medical management; P3 = CABG vs. medical management; other abbreviations as in Tables 1 and 2.

bypass graft conduits), and triage to revascularization versus medical therapy was an independent predictor of 1-year MACE.

ACS is common after CABG. In the Veterans Administration Cooperative Study of Coronary Artery Bypass Surgery, approximately 1 in 3 patients had an MI within 10

Table 4. Clinical Outcomes of Patients With Prior CABG Versus Without Prior CABG Triaged to PCI, (Repeat) CABG, or Medical Treatment

	Patients Triaged to PCI (n = 7,773)			Patients Triaged to CABG (n = 1,537)			Patients Triaged to Medical Treatment (n = 4,464)		
Outcomes	Prior CABG (n = 1,370)	No Prior CABG (n = 6,393)	p Value	Repeat CABG (n = 73)	First CABG (n = 1,464)	p Value	Prior CABG (n = 1,032)	No Prior CABG (n = 3,432)	p Value
At 30 days									
Death	1.4	1.0	0.19	12.4	3.6	0.0001	1.7	1.4	0.63
Cardiac death	1.2	0.8	0.25	12.4	3.4	<0.0001	1.2	1.0	0.65
Myocardial infarction	8.7	5.7	<0.0001	21.2	11.1	0.008	1.3	0.9	0.23
Q-wave	1.2	1.0	0.39	4.4	3.6	0.79	0.2	0.2	0.94
Non–Q-wave	7.4	4.8	<0.0001	16.8	7.6	0.003	1.1	0.7	0.17
Unplanned revascularization	3.8	3.4	0.50	0.0	1.6	0.29	2.1	1.0	0.005
MACE	11.9	8.2	<0.0001	28.8	14.2	0.0004	4.4	2.8	0.01
Non-CABG major bleeding	6.3	5.9	0.54	1.5	3.5	0.34	2.6	3.1	0.47
CABG major bleeding	—	—	0.68	61.6	53.3	0.21	0.1	0.5	0.07
NACE	16.2	12.7	0.0005	30.1	16.8	0.003	6.3	5.3	0.24
At 1 year									
Death	5.3	3.2	<0.0001	13.8	6.3	0.006	4.9	4.1	0.13
Cardiac death	3.0	1.8	0.002	13.8	4.5	0.0002	2.8	2.3	0.18
Myocardial infarction	13.5	8.2	<0.0001	21.2	11.8	0.014	4.6	2.2	<0.0001
Q-wave	1.6	1.8	0.94	4.4	3.7	0.81	0.6	0.4	0.47
Non–Q-wave	12.1	6.5	<0.0001	16.8	8.4	0.008	4.1	1.8	<0.0001
Unplanned revascularization	17.3	11.7	<0.0001	12.1	3.9	0.005	7.7	3.4	<0.0001
MACE	27.8	18.1	<0.0001	39.2	19.1	<0.0001	14.3	8.1	<0.0001

Values are %.

Abbreviations as in Tables 1, 2, and 3.

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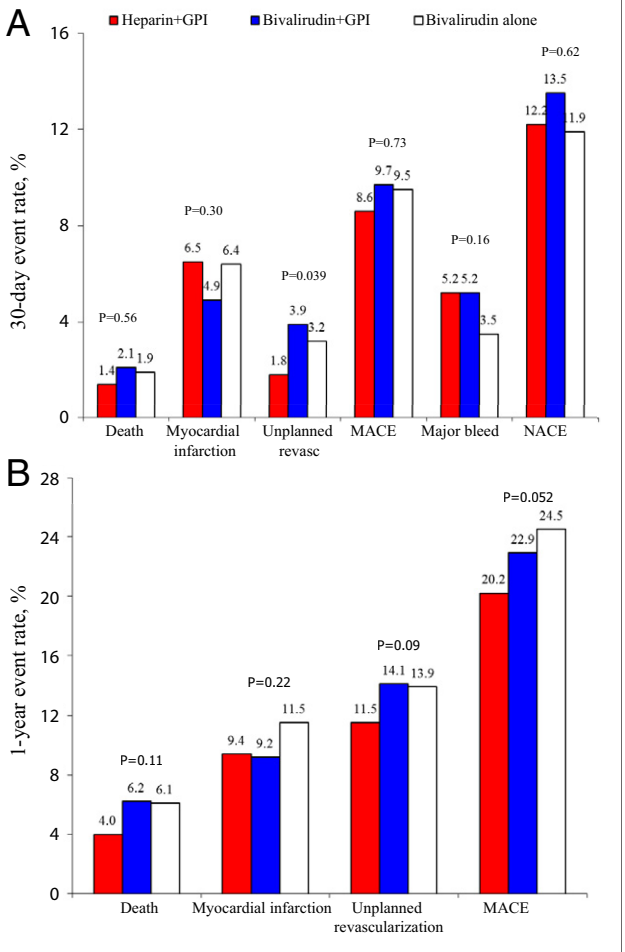

Figure 3. Outcomes of Patients With Prior CABG Randomized to Alternative Antithrombotic Regimens at 30 Days and 1 Year

Outcomes of patients with prior CABG randomized to alternative antithrombotic regimens at 30 days **(A)** and 1 year **(B)**. GPI = glycoprotein IIb/IIIa inhibitor; other abbreviations as in Figure 1.

years after CABG (3). In recent ACS reports, 12% to 22% of patients had prior CABG (11–16). In ACUITY, in which nearly 14,000 patients with moderate- and high-risk ACS were enrolled from 450 sites from 17 countries, 18% of patients had previously undergone CABG, which is consistent with these recent reports.

Clinical outcomes at 1 year in ACUITY were significantly worse in patients with prior CABG both by univariate and by multivariable analysis. Approximately 1 in 5 patients with prior CABG experienced a recurrent MACE by 1 year. Multiple factors underlie the poor prognosis of patients with prior CABG and ACS. Of note is the high-risk clinical profile of the prior CABG cohort, including older age, numerous comorbidities, and worse left ventricular function, which clearly contributed to adverse prognosis. More frequent occurrence of late MI and unplanned revascularization reflect more extensive atherosclerotic burden in the prior CABG cohort.

In addition, PCI of bypass graft conduits was associated with higher MACE rates than PCI in native coronary arteries, re-emphasizing that PCI of bypass grafts (especially saphenous vein grafts) (17) should be avoided if possible (i.e., look for alternative pathways for PCI in the native coronary arteries). Moreover, the use of arterial conduits was notably infrequent in ACS patients with prior CABG undergoing repeat CABG, likely due to clinical and anatomic factors (including urgency of reoperation, hemodynamic instability, and prior use of arterial grafts). Reoperation for bleeding and transfusions were also more common in patients undergoing repeat rather than first-time CABG. Thus, the early and late results of both repeat CABG and PCI in ACS are not as favorable as first-time surgery (18,19); this is consistent with prior reports in non-ACS patients (20,21).

Of note, triage to PCI, CABG, or medical therapy in ACUITY was not randomized, and the optimal management strategy when patients with prior CABG present with ACS remains undetermined. There was wide disparity in outcomes both between the triage arms and inside the medically treated patients stratified by reason to decline revascularization. The 6-month mortality of 3,853 ACS patients with prior CABG in the GRACE (Global Registry of Acute Coronary Events) was lower in patients revascularized versus those treated medically by univariate but not by multivariable analysis (14). In a larger Swedish registry of 10,837 patients with previous CABG, 1-year adjusted mortality was 50% lower with revascularization compared with medical management (16). In the AWESOME (Angina With Extremely Serious Operative Mortality Evaluation) trial, 3-year survival and freedom from recurrent ACS was similar among patients with prior CABG and refractory myocardial ischemia randomized to repeat CABG versus PCI, although they favored PCI in the patient-choice registry (18). In the present study, adjusted 30-day and 1-year rates of MACE were increased in patients treated with revascularization rather than medically. However, as all patients underwent angiography, it is likely that unmeasured confounders remain unaccounted for that guided the decision whether to revascularize. ACUITY thus highlights the poor prognosis of patients with prior CABG and ACS, regardless of the treatment pathway selected after angiography, and emphasizes the need for additional studies to refine optimal therapeutic approaches according to individual patient characteristics. These considerations notwithstanding, optimal medical therapy is of paramount importance whether revascularization is performed; intensive low-density lipoprotein cholesterol lowering in patients with previous CABG significantly reduced MACE and the need for repeat revascularization in 2 separate randomized trials (22,23). In ACUITY, at 1-year follow-up, the proportion of patients receiving statins

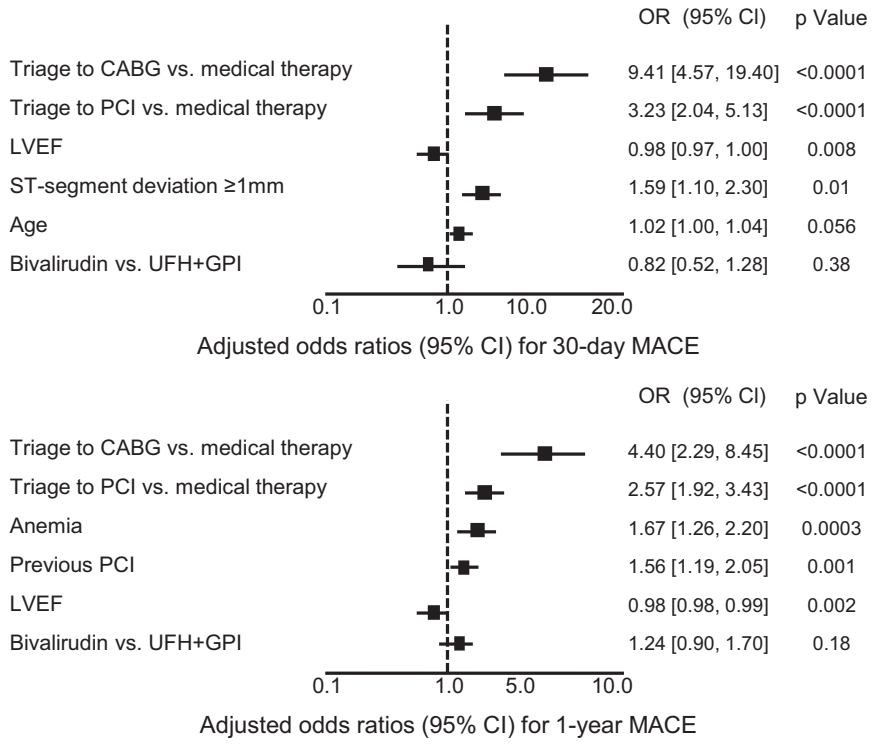

Figure 4. Multivariable Predictors of 30-Day and 1-Year MACE in Patients With Prior CABG

Multivariable predictors of 30-day **(A)** and 1-year **(B)** MACE in patients with prior CABG. CI = confidence interval; LVEF = left ventricular ejection fraction; OR = odds ratio; PCI = percutaneous coronary intervention; UFH = unfractionated heparin; other abbreviations as in Figure 1.

(78%) and other medications known to improve long-term outcomes in ACS was surprisingly low.

Finally, the optimal antithrombotic regimen for patients with ACS and prior CABG is not known, and existing data are conflicting. The impact of GPI in patients with ACS and prior CABG has been previously addressed in 2 post hoc analyses from the randomized trials, with opposite results (12,13). In ACUITY, by multivariable analysis, there were no significant differences in the 30-day or 1-year rates of MACE in patients with prior CABG treated with heparin plus a GPI or bivalirudin monotherapy.

Study limitations. Analysis of patients with a history of CABG was not pre-specified in the original trial design; therefore, these results should be considered hypothesis-generating. Important prognostic information related to CABG, such as the age, number, and type of bypass grafts, was not available. Triage to PCI, CABG, or medical management was determined on the basis of operator's discretion, and these results may vary between different operators and institutions. Follow-up longer than 1 year is necessary to fully characterize the outcomes of patients with ACS and prior CABG after different management strategies. Finally, a large-scale, randomized trial is necessary to truly determine the optimal management strategy for patients with prior CABG and ACS.

Conclusions

In the ACUITY trial, in which contemporary drugs and devices were used, patients with prior CABG presenting with ACS undergoing an early invasive strategy had a substantially worse prognosis than patients without prior CABG, especially if PCI or (repeat) CABG was required. Although bivalirudin monotherapy was an acceptable treatment for these patients, it did not improve their short-term or long-term prognoses. Further studies are required to identify therapeutic approaches to reduce MACE in patients with prior CABG and ACS.

Reprint requests and correspondence: Dr. Eugenia Nikolsky, Rambam Health Care Campus and the Technion, Department of Cardiology, Israel Institute of Technology, Bat Galim, 31096 Haifa, Israel. E-mail: enikolsky@gmail.com.

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