JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 69, NO. 4, 2017
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.10.067

SYNTAX Score and Long-Term Outcomes

The BARI-2D Trial

Fumiaki Ikeno, MD,[a] Maria Mori Brooks, PhD,[b] Kaori Nakagawa, MD,[a] Min-Kyu Kim, MD, PhD,[a] Hideaki Kaneda, MD, PhD,[a] Yoshiaki Mitsutake, MD, PhD,[a] Helen A. Vlachos, MS,[b] Leonard Schwartz, MD,[c] Robert L. Frye, MD,[d] Sheryl F. Kelsey, PhD,[b] Katsuhisa Waseda, MD, PhD,[a] Mark A. Hlatky, MD,[a,e] and the BARI-2D Study Group

ABSTRACT

BACKGROUND The extent of coronary disease affects clinical outcomes and may predict the effectiveness of coronary revascularization with either coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI). The SYNTAX (Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery) score quantifies the extent of coronary disease.

OBJECTIVES This study sought to determine whether SYNTAX scores predicted outcomes and the effectiveness of coronary revascularization compared with medical therapy in the BARI-2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial.

METHODS Baseline SYNTAX scores were retrospectively calculated for BARI-2D patients without prior revascularization ($N = 1,550$) by angiographic laboratory investigators masked to patient characteristics and outcomes. The primary outcome was major cardiovascular events (a composite of death, myocardial infarction, and stroke) over 5 years.

RESULTS A mid/high SYNTAX score (≥23) was associated with a higher risk of major cardiovascular events (hazard ratio: 1.36, confidence interval: 1.07 to 1.75, $p = 0.01$). Patients in the CABG stratum had significantly higher SYNTAX scores: 36% had mid/high SYNTAX scores compared with 13% in the PCI stratum ($p < 0.001$). Among patients with low SYNTAX scores (≤22), major cardiovascular events did not differ significantly between revascularization and medical therapy, either in the CABG stratum (26.1% vs. 29.9%, $p = 0.41$) or in the PCI stratum (17.8% vs. 19.2%, $p = 0.84$). Among patients with mid/high SYNTAX scores, however, major cardiovascular events were lower after revascularization than with medical therapy in the CABG stratum (15.3% vs. 30.3%, $p = 0.02$), but not in the PCI stratum (35.6% vs. 26.5%, $p = 0.12$).

CONCLUSIONS Among patients with diabetes and stable ischemic heart disease, higher SYNTAX scores predict higher rates of major cardiovascular events and were associated with more favorable outcomes of revascularization compared with medical therapy among patients suitable for CABG. (Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes; NCT00006305) (J Am Coll Cardiol 2017;69:395–403) © 2017 by the American College of Cardiology Foundation.

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From the [a]Division of Cardiovascular Medicine, Stanford University School of Medicine, Stanford, California; [b]Department of Epidemiology, University of Pittsburgh, Pittsburgh, Pennsylvania; [c]Division of Cardiology, University Health Network-Toronto General Hospital, Toronto, Ontario, Canada; [d]Division of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota; and the [e]Department of Health Research and Policy, Stanford University School of Medicine, Stanford, California. The BARI-2D trial is funded by the National Heart, Lung, and Blood Institute and the National Institute of Diabetes and Digestive and Kidney Diseases (U01 HL061744, U01 HL061746, U01 HL061748, U01 HL063804, R21-HL121495). BARI-2D receives significant supplemental funding from GlaxoSmithKline, Lantheus Medical Imaging, Inc. (formerly Bristol-Myers Squibb Medical Imaging, Inc.), Astellas Pharma US, Inc., Merck & Co., Inc., Abbott Laboratories, Inc., and Pfizer, Inc. Generous support is given by Abbott Laboratories Ltd., MediSense Products, Bayer Diagnostics, Becton, Dickinson and Company, J. R. Carlson Labs, Centocor, Inc., Eli Lilly and Company, ILipoScience, Inc., Merck Sante, Novartis Pharmaceuticals Corporation, and Novo Nordisk, Inc. Dr. Brooks has received a research grant from Gilead Sciences, Inc. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Ikeno, Brooks, Nakagawa, and Kim contributed equally to this work and are joint first authors. Patrick W. Serruys, MD, PhD, served as Guest Editor for this paper. A full listing of the BARI-2D Study Group can be found in the Online Appendix.

Manuscript received July 6, 2016; revised manuscript received October 1, 2016, accepted October 20, 2016.

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass graft

CI = confidence interval

HR = hazard ratio

MI = myocardial infarction

PCI = percutaneous coronary intervention

SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery

Coronary revascularization improves coronary blood flow, either by placing a conduit to bypass atherosclerotic obstructions in coronary artery bypass graft (CABG) surgery, or by expanding narrowed segments in percutaneous coronary intervention (PCI). Given this treatment mechanism, it seems likely that the clinical effectiveness of coronary revascularization should increase in proportion to the extent of underlying coronary disease, as suggested in early studies (1). The recently developed SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score characterizes the extent of coronary disease in terms of the number of lesions, their functional importance (2), and their complexity (3). Previous studies have categorized the SYNTAX score to identify patients at low (≤22), medium (23 to 32), and high risk (≥33) (4).

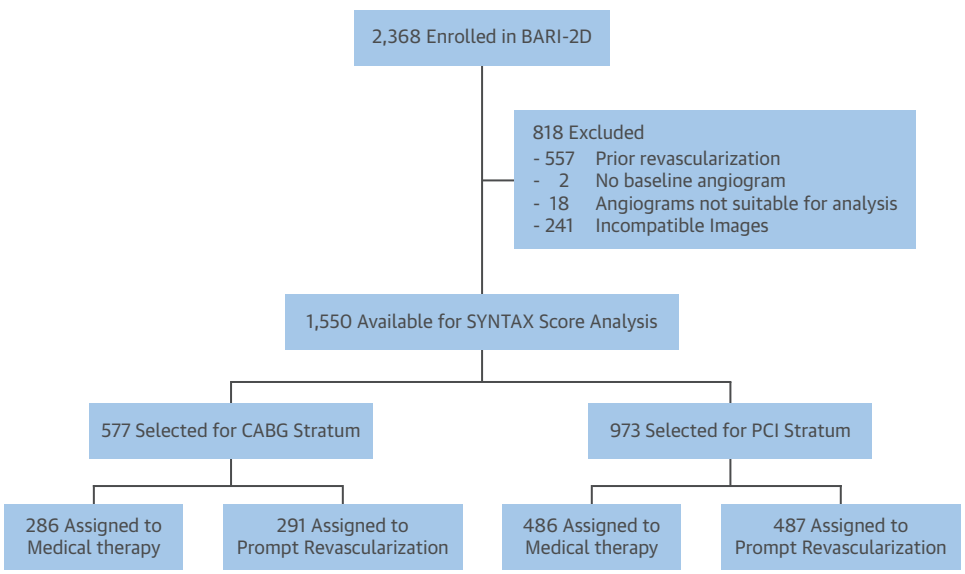
SEE PAGE 404

The BARI-2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial compared the strategies of: 1) adding prompt coronary revascularization to intensive medical therapy; and 2) intensive medical therapy alone among patients with type 2 diabetes mellitus and stable coronary disease (5). Randomization was stratified by the intended method of revascularization (PCI or CABG) declared before randomization. BARI-2D reported a significantly lower rate of the composite of all-cause death, myocardial infarction (MI), or stroke between revascularization and the medical strategy in the CABG stratum, but not in the PCI stratum (6). Patients in the CABG stratum had more extensive coronary disease, and it is possible that effect of revascularization is simply more pronounced among patients with the most extensive coronary disease. We sought to determine whether SYNTAX scores measured in BARI-2D patients could predict major cardiovascular events (death, MI, stroke), and hypothesized that revascularization would have greater effectiveness relative to medical therapy among patients with higher SYNTAX scores.

METHODS

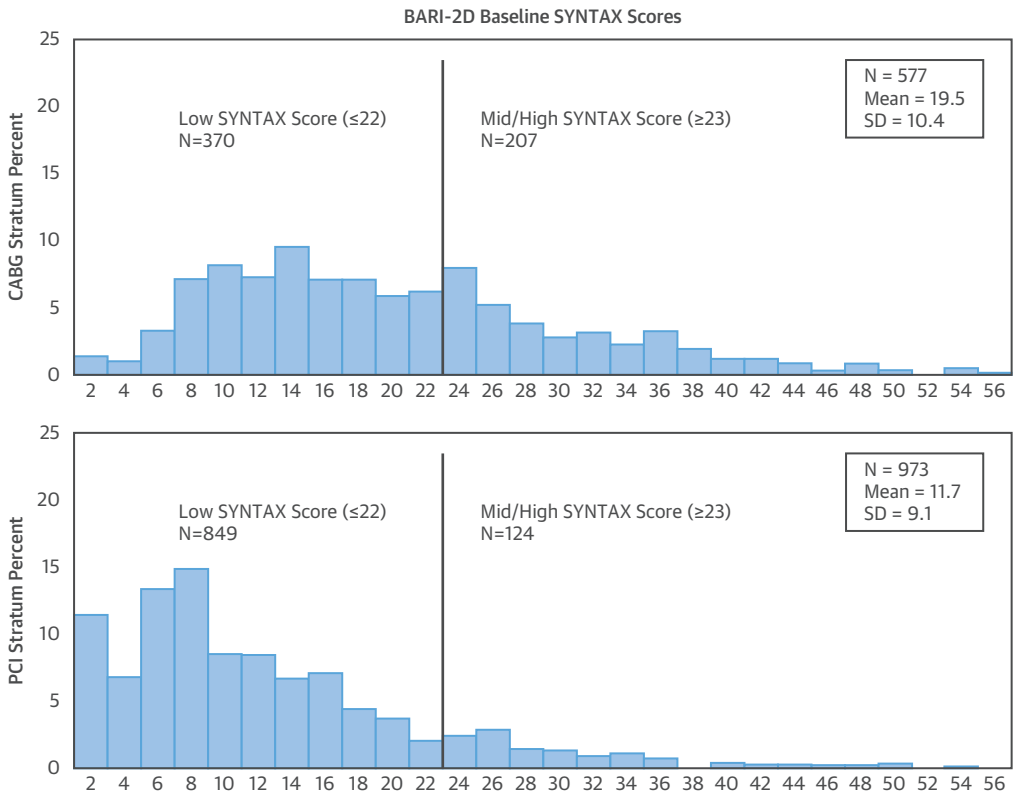
STUDY GROUP. The BARI-2D design, protocol, and patient characteristics have been described previously (6,7). Briefly, the BARI-2D trial was an international, multicenter trial comparing 2 major treatment approaches in a 2 × 2 factorial design: prompt coronary revascularization versus intensive medical therapy; and insulin sensitization versus insulin provision strategies. Patients with type 2 diabetes mellitus and evidence of myocardial ischemia were enrolled between January 1, 2001, and March 31, 2005.

FIGURE 1 Flow Diagram



Flowchart for patients included in the BARI-2D SYNTAX score analysis. BARI-2D = Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery.

FIGURE 2 Distribution of SYNTAX Scores



Distribution of SYNTAX scores in the 577 patients in the CABG stratum **(top)** and the 973 patients in the PCI stratum **(bottom)**. Abbreviations as in Figure 1.

The intended method of revascularization (PCI or CABG) was determined for each patient by the treating physician after coronary angiography, and randomization was stratified by the intended revascularization procedure. All patients were treated according to established clinical guidelines for lipid and blood pressure management, smoking cessation, physical activity, and weight loss.

Institutional review boards at the University of Pittsburgh and at each participating site approved the protocol. All patients provided written informed consent.

SYNTAX SCORE. The SYNTAX score was calculated from baseline angiograms by 2 interventional cardiologists at the BARI-2D angiographic laboratory who were masked to other information, including patient characteristics, therapies, and clinical outcomes. Intraobserver and interobserver reproducibility were assessed on 80 angiograms. SYNTAX scores were not computed for patients with a history of coronary revascularization before trial entry. SYNTAX scores ≤22 were categorized as low and scores ≥23 as mid/high, consistent with the prior published reports (4). Sensitivity analyses were conducted by: 1) using BARI-2D-specific tertiles of the SYNTAX scores; and 2) analyzing the SYNTAX score as a continuous variable.

PRIMARY AND SECONDARY OUTCOMES. The primary outcome for this analysis was major cardiovascular events, defined as the composite of all-cause death, MI, and stroke (the principal secondary endpoint in the BARI-2D trial). The secondary outcomes for this analysis were all-cause death (primary endpoint in the BARI-2D trial), cardiac death, and MI. All comparisons were performed over 5 years; the average follow-up was 5.3 years for death and 4.6 years for other outcomes. The BARI-2D trial was designed to have 88% power to detect a 30% reduction in the rate of death and 95% power to detect a 25% reduction in the rate of major cardiovascular events.

STATISTICAL ANALYSIS. Baseline demographic, clinical, and angiographic characteristics were

TABLE 1 Baseline Characteristics by SYNTAX Score

	Low SYNTAX Score (≤22) (n = 1,219)	Mid/High SYNTAX Score (≥23) (n = 331)	p Value
Age at study entry, yrs	62.0 (55.7–68.5)	63.3 (56.7–69.6)	0.032
Male	68.7 (837)	78.9 (261)	0.001
Race/ethnicity			
White non-Hispanic	65.5 (799)	69.2 (229)	0.286
Black non-Hispanic	17.6 (214)	13.3 (44)	
Hispanic	11.5 (140)	11.2 (37)	
Asian/other non-Hispanic	5.4 (66)	6.3 (21)	
Insulin-providing assignment	49.7 (606)	48.9 (162)	0.804
Sitting systolic BP	130.0 (118.7–143.3)	131.3 (116.7–143.3)	0.988
Sitting diastolic BP	75.3 (68.7–80.7)	74.0 (67.3–80.0)	0.319
BMI, kg/m^2	31.2 (27.5–35.0)	30.3 (27.1–33.4)	0.009
Hypertension requiring therapy	81.8 (985)	80.6 (261)	0.605
History of cigarette smoking	64.1 (779)	64.2 (212)	0.952
History of MI	21.8 (261)	33.4 (109)	0.001
History of CHF requiring therapy	5.6 (68)	4.2 (14)	0.328
Duration of DM	8.1 (3.4–14.6)	8.7 (4.0–16.0)	0.131
HbA_{1c} %	7.30 (6.50–8.60)	7.30 (6.40–8.45)	0.717
LDL, mg/dl	93.0 (74.0–116.0)	93.0 (74.0–118.0)	0.894
HDL, mg/dl	37.0 (31.0–43.0)	36.0 (32.0–42.0)	0.451
Total cholesterol, mg/dl	165.0 (141.0–193.0)	165.5 (142.0–193.0)	0.913
eGFR (MDRD algorithm), ml/min/1.73 m^2	77.1 (63.9–91.7)	76.8 (61.1–93.5)	0.706
Currently taking insulin	26.9 (327)	24.2 (80)	0.319
Cerebrovascular accident or TIA	8.7 (106)	9.5 (31)	0.684
Chronic renal dysfunction	2.1 (26)	2.5 (8)	0.733
Any major ECG abnormalities	28.3 (335)	29.6 (96)	0.631
Baseline Q waves	10.3 (125)	12.1 (40)	0.338
Baseline ST-segment depression	1.8 (22)	2.7 (9)	0.292
Baseline ST-segment elevation	4.8 (58)	5.1 (17)	0.776
Site: LVEF <50%	14.7 (174)	18.8 (61)	0.067
Number of vessels with lesions ≥50%			
1	45.2 (550)	14.5 (48)	0.001
2	35.8 (436)	40.2 (133)	
3	19.0 (231)	45.3 (150)	
Number of lesions	4.0 (3.0–6.0)	6.0 (4.0–7.0)	0.001
Lesions ≥50% stenosis	2.0 (1.0–3.0)	3.0 (2.0–5.0)	0.001
Myocardial jeopardy	40.0 (24.0–58.0)	65.0 (48.0–76.0)	0.001
Proximal LAD ≥50% stenosis	9.8 (119)	19.6 (65)	0.001
Total occlusions	44.2 (161)	55.6 (110)	0.010

Values are median (interquartile range) or % (n).

BMI = body mass index; BP = blood pressure; CHF = congestive heart failure; DM = diabetes mellitus; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HbA_{1c} = glycosylated hemoglobin; HDL = high-density lipoprotein; LAD = left anterior descending; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction; MDRD = Modification of Diet in Renal Disease; MI = myocardial infarction; SYNTAX = Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery; TIA = transient ischemic attack.

summarized using proportions, means, or medians, and compared using chi-square statistics for categorical variables and Wilcoxon rank sum tests for continuous variables. Kaplan-Meier cumulative event rates were used to describe outcomes during follow-up. Hazard ratios (HRs) with 95% confidence intervals (CIs) from Cox proportional hazards regression models were used to compare the risk of major cardiovascular events between SYNTAX score groups (low vs. mid/high) and between the assigned treatment strategies within subgroups defined by the SYNTAX scores according to randomization stratum. Hazard ratios for mid/high SYNTAX score versus low SYNTAX score were adjusted for: revascularization assignment; insulin assignment; age; sex; history of MI; history of heart failure; insulin at baseline; and estimated glomerular filtration rate <60 ml/min/1.73 m^2. The proportionality assumption for SYNTAX score and for treatment assignment was tested in each model by adding an interaction between the variable and time. All analyses comparing assigned treatments were performed using the intention-to-treat principle. Intraobserver and interobserver variability were evaluated using kappa statistics.

RESULTS

STUDY SAMPLE. Of the 2,368 patients enrolled in BARI-2D, 818 were excluded from this analysis: 557 had prior coronary revascularization; 2 did not have a baseline angiogram available; 18 had angiograms of insufficient quality to compute a SYNTAX score; and 241 patients had angiograms that could not be evaluated because of an incompatible Digital Imaging and Communications in Medicine format (Figure 1). SYNTAX scores were calculated for 1,550 patients (65.5%), with excellent intraobserver (kappa statistic = 0.97) and interobserver (kappa statistic = 0.83) reproducibility, similar to a previous study (8). BARI-2D patients with measured SYNTAX scores had less comorbidity than patients whose SYNTAX scores were not measured (Online Table 1).

SYNTAX SCORE. The mean SYNTAX score in the 1,550 study patients was 14.6 ± 10.3, range 0 to 54). Most patients (1,219) had a low SYNTAX score, and 331 had a mid/high score. The mean SYNTAX score was significantly higher in the CABG stratum (19.5 ± 10.4) than in the PCI stratum (11.7 ± 9.1; p < 0.001), and more patients in the CABG stratum had mid/high SYNTAX scores (36% vs. 13%, p < 0.001) (Figure 2).

Baseline characteristics were generally similar between patients who had low versus mid/high SYNTAX scores (Table 1), apart from the expected differences in the numbers of diseased vessels, lesions and total occlusions, and the myocardial jeopardy score (9). Within the CABG and PCI strata, baseline characteristics were similar between patients with low versus mid/high SYNTAX scores, apart from expected differences in the severity and extent of coronary disease (Table 2).

Through 5.0 years of follow-up, major cardiovascular events occurred in 301 patients: 166 patients died, 150 had at least 1 acute MI, and 38 had at least

TABLE 2 Baseline Characteristics by Revascularization Stratum and SYNTAX Score

	CABG Stratum			PCI Stratum		
	Low SYNTAX Score (≤22) (n = 370)	Mid/High SYNTAX Score (≥23) (n = 207)	p Value	Low SYNTAX Score (≤22) (n = 849)	Mid/High SYNTAX Score (≥23) (n = 124)	p Value
Age at study entry, yrs	63.4 (57.9–68.9)	64.7 (57.8–70.1)	0.198	61.2 (55.2–68.2)	61.5 (55.5–68.1)	0.734
Male	74.6 (276)	81.6 (169)	0.053	66.1 (561)	74.2 (92)	0.072
Race/ethnicity						
White non-Hispanic	68.9 (255)	75.4 (156)	0.424	64.1 (544)	58.9 (73)	0.232
Black non-Hispanic	11.4 (42)	8.7 (18)		20.3 (172)	21.0 (26)	
Hispanic	13.8 (51)	11.6 (24)		10.5 (89)	10.5 (13)	
Asian/other non-Hispanic	5.9 (22)	4.3 (9)		5.2 (44)	9.7 (12)	
Insulin-providing assignment	49.5 (183)	45.4 (94)	0.351	49.8 (423)	54.8 (68)	0.297
Sitting systolic BP, mm Hg	132.7 (120.0–147.0)	132.0 (120.0–145.3)	0.528	130.0 (118.0–141.3)	128.7 (113.3–142.3)	0.580
Sitting diastolic BP, mm Hg	76.7 (70.0–82.0)	74.7 (68.7–81.3)	0.184	74.7 (67.3–80.0)	71.3 (65.0–79.3)	0.095
BMI	29.6 (26.7–33.9)	30.2 (27.1–33.3)	0.480	31.9 (28.0–35.7)	30.6 (27.2–33.6)	0.011
Hypertension requiring therapy	83.6 (306)	81.7 (165)	0.560	81.0 (679)	78.7 (96)	0.541
History of cigarette smoking	63.8 (236)	66.5 (137)	0.512	64.2 (543)	60.5 (75)	0.424
History of MI	30.1 (110)	34.3 (70)	0.304	18.1 (151)	32.0 (39)	0.001
History of CHF requiring therapy	4.9 (18)	3.9 (8)	0.578	5.9 (50)	4.8 (6)	0.631
Duration of DM	8.8 (3.5–15.4)	8.7 (4.0–15.6)	0.585	7.8 (3.4–14.1)	9.1 (3.9–16.4)	0.229
HbA_{1c} %	7.40 (6.40–8.80)	7.50 (6.50–8.50)	0.819	7.30 (6.50–8.40)	7.20 (6.30–8.20)	0.236
LDL, mg/dl	95.5 (73.0–122.0)	94.0 (75.0–117.0)	0.515	92.0 (74.0–115.0)	90.0 (70.0–123.0)	0.937
HDL, mg/dl	37.0 (32.0–43.0)	36.0 (32.0–42.5)	0.987	37.0 (31.0–43.0)	36.0 (32.0–42.0)	0.407
Total cholesterol, mg/dl	168.0 (143.0–198.0)	167.0 (144.0–192.5)	0.422	165.0 (141.0–190.0)	162.0 (136.0–193.0)	0.930
eGFR (MDRD algorithm), ml/min/1.73 m^2	75.7 (63.5–89.7)	73.7 (60.2–89.9)	0.616	78.0 (64.3–92.9)	79.7 (63.5–98.2)	0.306
Currently taking insulin	21.1 (78)	21.3 (44)	0.974	29.4 (249)	29.0 (36)	0.934
Cerebrovascular accident or TIA	7.0 (26)	6.4 (13)	0.759	9.5 (80)	14.5 (18)	0.082
Chronic renal dysfunction	1.9 (7)	1.5 (3)	0.709	2.2 (19)	4.1 (5)	0.220
Any major ECG abnormalities	39.4 (143)	33.5 (68)	0.164	23.4 (192)	23.1 (28)	0.958
Baseline Q waves	15.4 (57)	15.0 (31)	0.891	8.0 (68)	7.3 (9)	0.772
Baseline ST-segment depression	3.2 (12)	3.4 (7)	0.929	1.2 (10)	1.6 (2)	0.682
Baseline ST-segment elevation	6.2 (23)	5.8 (12)	0.840	4.1 (35)	4.0 (5)	0.962
Site: LVEF <50%	15.7 (57)	17.6 (36)	0.539	14.2 (117)	20.8 (25)	0.059
Number of vessels with lesions ≥50%						
1	18.1 (67)	10.6 (22)	0.001	57.0 (483)	21.0 (26)	0.001
2	47.3 (175)	38.2 (79)		30.8 (261)	43.5 (54)	
3	34.6 (128)	51.2 (106)		12.2 (103)	35.5 (44)	
Number of lesions	5.0 (4.0–7.0)	6.0 (5.0–7.0)	0.002	4.0 (2.0–5.0)	5.0 (4.0–6.0)	0.001
Lesions ≥50% stenosis	3.0 (2.0–4.0)	4.0 (3.0–5.0)	0.001	2.0 (1.0–3.0)	3.0 (2.0–4.0)	0.001
Myocardial jeopardy	57.0 (41.0–74.0)	68.0 (52.0–79.0)	0.001	33.0 (20.0–48.0)	55.0 (41.5–72.0)	0.001
Proximal LAD ≥50% stenosis	14.9 (55)	23.2 (48)	0.012	7.6 (64)	13.7 (17)	0.021
Total occlusions	44.4 (156)	55.8 (110)	0.010	38.5 (5)	0.0 (0)	0.439

Values are median (interquartile range) or % (n).
CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; other abbreviations as in Table 1.

1 stroke. Patients with mid/high SYNTAX scores had significantly greater risk of major cardiovascular events at 5 years than patients with low SYNTAX scores (25.6% vs. 21.4%, p = 0.014). Most individual components of the composite primary endpoint were also higher among patients with mid/high SYNTAX scores compared with those who had low SYNTAX scores, including all-cause death (15.2% vs. 10.7%, p = 0.0085), cardiac death (8.6% vs. 4.5%, p = 0.005), and MI (13.7 vs. 10.6%, p = 0.04), although stroke was not significantly different (2.3% vs. 3.1%, p = 0.33). After adjustment for key demographic and clinical risk factors, a mid/high SYNTAX score remained significantly associated with a greater risk of major cardiovascular events (HR: 1.34, p = 0.02), death (HR: 1.43, p = 0.03), cardiac death (HR: 2.05, p = 0.003), and MI (HR: 1.44, p = 0.05) (Table 3).

Among the 28 proportional hazards tests run, the proportional hazards assumption was rejected (p < 0.05) only once: the model predicting death/MI/stroke by SYNTAX score categories in the PCI stratum. The difference in the risk of death/MI/

TABLE 3 Risk of Cardiovascular Events for Mid/High SYNTAX Score (≥23) Compared With Low SYNTAX Score (≤22)

	Unadjusted HR	95% CI	p Value	Adjusted HR*	95% CI	p Value
Combined strata (n = 1,550)						
Death/MI/stroke	1.36	1.07–1.75	0.014	1.34	1.04–1.73	0.02
Death	1.52	1.11–2.09	0.009	1.43	1.04–1.98	0.03
Cardiac death	1.92	1.21–3.05	0.006	2.05	1.28–3.30	0.003
MI	1.44	1.02–2.04	0.041	1.44	1.01–2.05	0.05
CABG stratum (n = 577)						
Death/MI/stroke	0.87	0.61–1.24	0.431	0.81	0.57–1.17	0.265
Death	1.12	0.72–1.73	0.614	1.03	0.66–1.61	0.896
Cardiac death	1.20	0.65–2.22	0.563	1.17	0.63–2.18	0.620
MI	0.77	0.45–1.31	0.335	0.74	0.43–1.27	0.277
PCI stratum (n = 973)						
Death/MI/stroke	1.99	1.40–2.82	0.001	2.16	1.51–3.09	0.001
Death	1.84	1.14–2.96	0.013	1.96	1.20–3.20	0.007
Cardiac death	2.56	1.24–5.27	0.011	2.94	1.38–6.23	0.005
MI	2.47	1.56–3.93	0.001	2.56	1.59–4.12	0.001

*HR for mid/high SYNTAX score versus low SYNTAX score adjusted for: revascularization assignment, insulin assignment, age, sex, history of MI, history of CHF, insulin at baseline, and eGFR <60 ml/min/1.73 m^2.

CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 1 and 2.

stroke between the 2 SYNTAX groups was larger earlier after randomization compared with later follow-up. Thus, the HR in this model should be interpreted as the average HR over the 5 years of follow-up, and may not apply to individual time points.

REVASCULARIZATION VERSUS MEDICAL THERAPY. The effect of coronary revascularization compared with medical therapy varied according to SYNTAX score and stratum of intended revascularization. In the CABG stratum, there was no significant difference in the 5-year rate of major cardiovascular events between the revascularization and the medical strategies in patients with a low SYNTAX score (26.1% vs. 29.9%, p = 0.41) (**Central Illustration, panel A**), whereas in patients with a mid/high SYNTAX score, there was a significantly lower incidence of major cardiovascular events in the patients assigned to revascularization (15.3% vs. 30.3%, p = 0.017) (**Central Illustration, panel B**). In the PCI stratum, the rate of major cardiovascular events did not differ significantly between patients assigned to revascularization or medical therapy (**Central Illustration, panels C and D**) in either the low-SYNTAX score subgroup (17.8% vs. 19.2%, p = 0.84) or the mid/high-SYNTAX score subgroup (35.6% vs. 26.5%, p = 0.12). All of the cardiovascular outcomes by treatment assignment are summarized in Online Table 2.

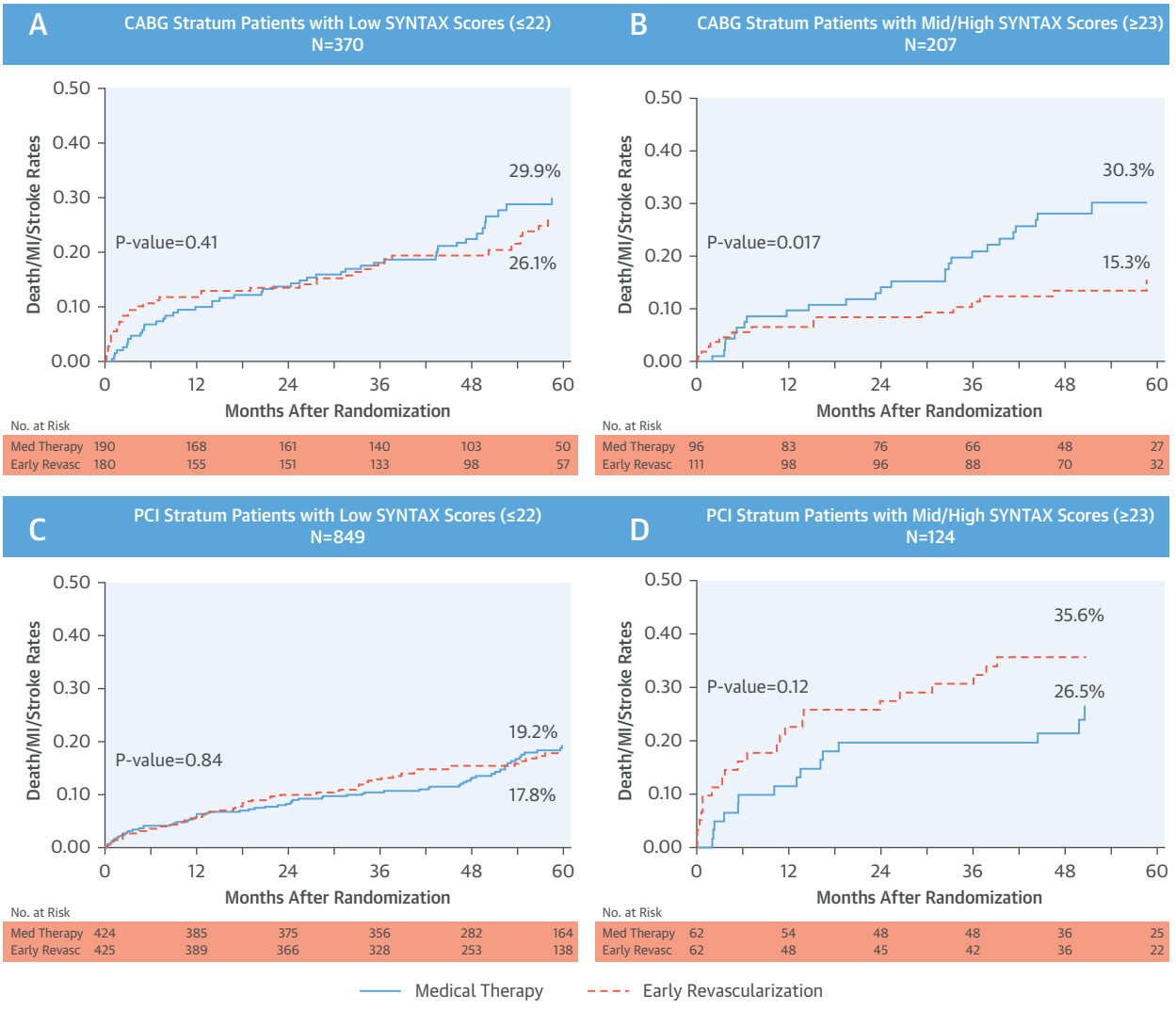
In multivariable adjusted models, assignment to revascularization in the CABG stratum was associated with a significantly lower risk of major cardiovascular events in the mid/high SYNTAX patients (adjusted HR: 0.46, p = 0.01), but not in the low SYNTAX patients (adjusted HR: 0.88, p = 0.56). The interaction test indicated that these 2 treatment HRs were marginally different from each other (p = 0.08) (**Table 4**). This pattern was similar for individual components of the composite outcome, and most pronounced for acute MI (**Table 4**). Assignment to revascularization in the PCI stratum was associated with a nonsignificantly higher risk of major cardiovascular events in the mid/high-SYNTAX subgroup (adjusted HR: 1.69, p = 0.11), with similar outcomes in the low-SYNTAX subgroup (adjusted HR: 0.96, p = 0.82, interaction p = 0.13). This pattern was again similar for the individual outcomes (**Table 4**). Results of the sensitivity analyses using BARI-2D-specific tertiles (≤7, 8 to 15, and ≥16) (Online Tables 3 to 5) were consistent with primary analysis. Results were also consistent when the SYNTAX score was analyzed as a continuous variable, rather than a categorical variable (Online Tables 6 and 7).

DISCUSSION

This study confirms that the SYNTAX score, a measure of the extent and severity of coronary disease, predicts long-term clinical outcomes in patients with diabetes and coronary disease. The adverse effect on prognosis of more extensive coronary disease has been shown in many studies, although generally using less sophisticated measures. The number of diseased vessels, the Gensini score, and the Duke Anatomy score have all been shown to predict long-term outcomes, consistent with hypothesis that plaque rupture and coronary events are more likely when coronary disease is more extensive (1,10,11). The myocardial jeopardy index, which was used in the BARI and BARI-2D trials, also predicts worse outcomes (9).

The key observation from this study is that higher levels of the SYNTAX score predict particular therapeutic benefit from CABG compared with medical therapy. We found a far more striking reduction in major cardiovascular events in patients with medium or high SYNTAX scores (HR: 0.46) than in patients with low SYNTAX scores (HR: 0.88). This observation is consistent with earlier studies that found a greater survival benefit from CABG compared with medical therapy for patients with 3-vessel or left main disease (1,12). Higher SYNTAX scores were also predictive of benefit from CABG compared with PCI in the SYNTAX trial (13). Recent studies using SYNTAX score report differing findings about the capacity of the SYNTAX score to predict adverse events among patients

CENTRAL ILLUSTRATION **5-Year Major Cardiovascular Event-Free Survival**



Ikeno, F. et al. J Am Coll Cardiol. 2017;69(4):395-403.

Kaplan-Meier estimates for the composite outcome of death/MI/stroke, comparing patients assigned to medical therapy **(blue solid line)** with patients assigned to revascularization **(orange dashed line)** over 5 years of follow-up. **(A)** Patients in the CABG stratum with low SYNTAX scores. **(B)** Patients in the CABG stratum with mid/high SYNTAX scores. **(C)** Patients in the PCI stratum with low SYNTAX scores. **(D)** Patients in the PCI stratum with mid/high SYNTAX scores. Interaction p values were 0.08 in the CABG stratum **(A, B)** and 0.13 in the PCI stratum **(C, D)**. CABG = coronary artery bypass graft; MI = myocardial infarction; PCI = percutaneous coronary intervention; SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery.

undergoing CABG (14-16). Potential explanations include different study designs, patient populations, therapies, limited follow-up period, and the interobserver and intraobserver variability of the SYNTAX score. Further studies, such as the ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches; NCT01471522) trial, could test whether CABG is particularly effective in reducing the risk of major cardiovascular events among patients who have the most extensive coronary disease.

The effect of PCI compared with medical therapy on major cardiac events among patients with stable ischemic heart disease has been less certain (17,18). In BARI-2D, patients in the PCI stratum had no overall benefit from revascularization with PCI compared with

TABLE 4 Revascularization Versus Medical Therapy By Revascularization Stratum and SYNTAX Score

Outcome Variable	SYNTAX Score	Adjusted HR*	95% CI	p Value	Interaction p Value†
CABG stratum (N = 577)					
Death/MI/stroke	Low (≤22)	0.88	0.58-1.35	0.56	0.08
	Mid/high (≥23)	0.46	0.25-0.85	0.01	
Death	Low (≤22)	0.90	0.52-1.58	0.72	0.57
	Mid/high (≥23)	0.70	0.35-1.41	0.32	
Cardiac death	Low (≤22)	1.03	0.47-2.29	0.94	0.56
	Mid/high (≥23)	0.72	0.27-1.89	0.50	
MI	Low (≤22)	0.80	0.44-1.45	0.46	0.04
	Mid/high (≥23)	0.21	0.07-0.64	0.01	
PCI stratum (N = 973)					
Death/MI/stroke	Low (≤22)	0.96	0.70-1.34	0.82	0.13
	Mid/high (≥23)	1.69	0.89-3.19	0.11	
Death	Low (≤22)	1.01	0.65-1.56	0.97	0.13
	Mid/high (≥23)	2.23	0.89-5.58	0.09	
Cardiac death	Low (≤22)	1.13	0.52-2.45	0.77	0.22
	Mid/high (≥23)	3.09	0.77-12.31	0.11	
MI	Low (≤22)	0.95	0.59-1.52	0.82	0.23
	Mid/high (≥23)	1.68	0.74-3.82	0.21	

*HR for revascularization versus medical adjusted for: IS/IP assignment, age, sex, history of MI, history of CHF, insulin use at baseline, and eGFR <60 ml/min/1.73 m^2. †Testing hypothesis of equivalence of HRs for revascularization versus medical therapy in the mid/high SYNTAX and low SYNTAX strata.

IS/IP = insulin sensitizing/ insulin providing; other abbreviations as in Tables 1 to 3.

medical therapy. The present study extends this finding by examining whether higher SYNTAX scores might identify patients who would receive more benefit from PCI. Contrary to our a priori hypothesis, higher SYNTAX scores identified patients who had somewhat worse outcomes after PCI. Although this trend was of only borderline significance, it was in the opposite direction from what we expected. This finding may reflect the need for multiple dilations and stent implantations for patients with higher SYNTAX scores, each of which may be susceptible to late complications, including restenosis and stent thrombosis. There were relatively few patients with mid/high SYNTAX scores in the PCI stratum in our study, however, so it is difficult to draw definitive conclusions on this question. The ISCHEMIA study has enrolled patients with more than moderate ischemia, uses contemporary treatment, and ought to clarify the comparative effectiveness of an invasive strategy using PCI.

The BARI-2D trial did not randomize patients to CABG or PCI, so no direct comparison of these 2 forms of revascularization can be made here. The finding that CABG particularly benefited patients with high SYNTAX scores is consistent with the results of several randomized trials directly comparing CABG and PCI, including SYNTAX and FREEDOM (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) (19).

STUDY LIMITATIONS. Patients in the BARI-2D trial were highly selected, and all patients had diabetes mellitus, so the results may not apply to patients without diabetes. PCI procedures in BARI-2D used bare-metal or first-generation drug-eluting stents. Patients with left main coronary disease and patients with single-vessel disease were excluded from BARI-2D, so we were unable to examine the extremes of the SYNTAX score. SYNTAX scores were obtained on only a subset (65%) of patients enrolled in the BARI-2D trial, and the patients whose scores could not be measured were somewhat less severely ill than the patients in the analysis. Although adding clinical variables to the SYNTAX score could improve decision-making in the clinical setting, our hypothesis was that extent of anatomic features would predict treatment benefit in BARI-2D. Therefore, we did not examine the prognostic capability of the SYNTAX score II (20), which can be examined in a future study. It would be interesting to assess the residual SYNTAX score after PCI (21-23); however, because it is impossible to compute the residual SYNTAX score in patients treated with CABG, we could not assess its impact in this study. Of note, the main comparison of the BARI-2D study was revascularization versus medical therapy. The SYNTAX score was originally developed to predict major adverse cardiac events, a composite outcome that includes repeat revascularization. In the current study (and in contrast to previous studies, including the SYNTAX trial) we did not assess repeat revascularization as an outcome because our focus was on hard cardiac events.

CONCLUSIONS

CABG, PCI, and medical therapy all had similar cardiovascular outcomes among patients with low SYNTAX scores (≤22) who had diabetes mellitus, stable ischemic heart disease, and no prior coronary revascularization. Among patients with mid or high SYNTAX scores (≥23), coronary revascularization with CABG significantly reduced the rate of major cardiovascular events during 5 years of follow-up.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Fumiaki Ikeno, Department of Cardiology, Stanford University, 300 Pasteur Drive, FALK CVRB CV-007, Stanford, California 94305. E-mail: fikeno@stanford.edu.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The SYNTAX score is a useful tool for determining the need and optimal strategy for coronary revascularization in patients with diabetes mellitus and stable ischemic heart disease. In those with higher SYNTAX scores, surgical revascularization is associated with lower rates of major cardiovascular events than medical therapy alone.

TRANSLATIONAL OUTLOOK: The results of ongoing clinical trials are expected to enhance the selection of patients with stable ischemic heart disease who are likely to gain the greatest benefit from revascularization.

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KEY WORDS angiography, coronary disease, ischemia, prognosis, stents, surgery

APPENDIX For a full listing of the BARI-2D Study Group as well as supplemental tables, please see the online version of this article.