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Individualizing Revascularization Strategy for Diabetic Patients With Multivessel Coronary Disease

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ABSTRACT

BACKGROUND In patients with diabetes and multivessel coronary artery disease (CAD), the FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trial demonstrated that, on average, coronary artery bypass grafting (CABG) was superior to percutaneous coronary intervention (PCI) for major acute cardiovascular events (MACE) and angina reduction. Nonetheless, multivessel PCI remains a common revascularization strategy in the real world.

OBJECTIVES To translate the results of FREEDOM to individual patients in clinical practice, risk models of the heterogeneity of treatment benefit were built.

METHODS Using patient-level data from 1,900 FREEDOM patients, the authors developed models to predict 5-year MACE (all-cause mortality, nonfatal myocardial infarction, and nonfatal stroke) and 1-year angina after CABG and PCI using baseline covariates and treatment interactions. Parsimonious models were created to support clinical use. The models were internally validated using bootstrap resampling, and the MACE model was externally validated in a large real-world registry.

RESULTS The 5-year MACE occurred in 346 (18.2%) patients, and 310 (16.3%) had angina at 1 year. The MACE model included 8 variables and treatment interactions with smoking status (c = 0.67). External validation in stable CAD (c = 0.65) and ACS (c = 0.68) demonstrated comparable performance. The 6-variable angina model included a treatment interaction with SYNTAX score (c = 0.67). PCI was never superior to CABG, and CABG was superior to PCI for MACE in 54.5% of patients and in 100% of patients with history of smoking.

CONCLUSIONS To help disseminate the results of FREEDOM, the authors created a personalized risk prediction tool for patients with diabetes and multivessel CAD that could be used in shared decision-making for CABG versus PCI by estimating each patient's personal outcomes with both treatments. (J Am Coll Cardiol 2019;74:2074–84)

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Based on a number of clinical trials of patients with diabetes and multivessel coronary artery disease (CAD) (1), guidelines recommend treatment with coronary artery bypass grafting surgery (CABG) over multivessel percutaneous coronary intervention (PCI) (2). As PCI techniques have improved with fewer procedural complications and less restenosis, this recommendation has continued to be challenged. Most recently, however, the FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trial (3) again demonstrated superiority of CABG over PCI among these patients for both long-term major adverse cardiovascular events (MACE) and patient health status; their symptoms, function, and quality of life (4). Despite these results, and continued guideline recommendations, multivessel PCI has remained a common revascularization strategy in patients with diabetes and multivessel disease (5,6).

Barriers to the adoption of this guideline may include patients' preference for a less-invasive approach (7,8), lack of appropriate shared decision-making, and overestimation of surgical risk by physicians (9). Moreover, treatment options are usually presented by the treating physician, who may be biased in overestimating or underestimating the benefits and harms of a particular revascularization strategy (PCI and/or CABG), depending on their specialty, experience, and background. A more evidence-based infrastructure is therefore needed so that the risks and benefits of each approach could be transparently shared and used as a foundation for shared decision-making. As such, we leveraged the FREEDOM trial data to develop prediction models for both long-term MACE and angina, after both CABG and PCI, among patients with diabetes and multivessel CAD and sought to validate the former of these in a contemporary observational registry.

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METHODS

THE FREEDOM TRIAL. The FREEDOM trial (3) was an international, multicenter, randomized clinical trial that compared multivessel PCI with CABG in patients with diabetes and multivessel CAD who were on optimal medical therapy. The design, protocol, and methods of the FREEDOM trial (10) and the clinical (3) and health status (4) outcomes have been previously published. Briefly, between April 2005 and April 2010, adult patients with diabetes and angiographically confirmed multivessel CAD (70% stenosis in 2 or more major epicardial vessels involving at least 2 separate coronary territories but without left main stenosis) and an appropriate indication for revascularization were randomized on a 1:1 basis to undergo revascularization by CABG or multivessel PCI with first-generation DES. All patients were recommended to continue aspirin and clopidogrel for at least 12 months after stent placement. Patients with prior cardiac surgery and patients with PCI or stroke within the last 6 months were excluded. The median follow-up for the FREEDOM study was 3.8 years (minimum of 2 years). Each participating site obtained institutional research board approval, and all patients provided informed consent. The FREEDOM trial was registered at the Clinical Trials website (NCT00086450).

ASSESSMENT OF OUTCOMES IN FREEDOM. The primary outcome of the FREEDOM trial was MACE, which was defined as a composite of all-cause death, nonfatal myocardial infarction (MI), and nonfatal stroke (3)—events that were formally adjudicated by an independent committee. All patients underwent routine assessment for neurological status and cardiac markers at each of the follow-up visits to facilitate adjudication. Adjudicated 5-year MACE was the outcome of the first model created from FREEDOM.

Because the 2 goals of CAD treatment are to prevent MACE and to improve angina, we also constructed a model of being angina-free 1 year after treatment. Angina was assessed at baseline (prior to randomization), at 1, 6, and 12 months after randomization, and annually thereafter using the Seattle Angina Questionnaire (SAQ). The SAQ is a reliable and valid 19-item questionnaire with a 4-week recall period that measures 5 domains of health in patients with CAD: angina frequency (SAQ AF), angina stability, quality of life, physical limitation, and treatment satisfaction (11,12). Linguistically and culturally validated translations in each patient's native language were used. Domain scores range from 0 to 100, with higher scores indicating fewer symptoms and better quality of life. For this particular analysis, we focused on the SAQ AF, which has been shown to correlate closely with daily angina diaries (13). Congruent with prior work, angina was categorized as none (SAQ AF score = 100) or any (SAQ AF score <100) (14), and we developed a model to predict having angina at 1 year.

STATISTICAL ANALYSIS. Demographic and clinical characteristics were compared between patients with and without MACE at 5 years and those with and without angina at 1 year using independent Student's

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CABG = coronary artery bypass grafting

CAD = coronary artery disease

MACE = major acute cardiovascular events

MI = myocardial infarction

PCI = percutaneous coronary intervention

SAQ = Seattle Angina Questionnaire

TABLE 1 Demographic and Clinical Characteristics of Patients With or Without MACE at 5 Years and of Patients With or Without Angina at 1 Year

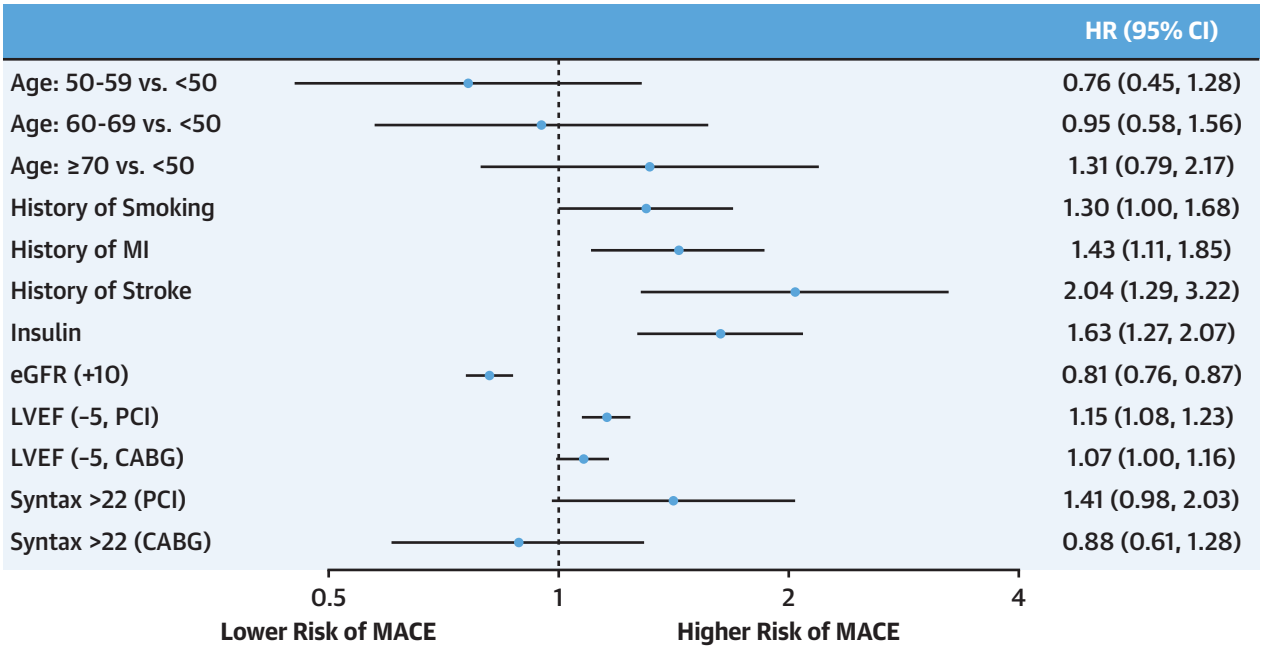
	MACE at 5 Yrs			Any Angina at 1 Yr*		
	Yes (n = 346)	No (n = 1,554)	p Value	Yes (n = 310)	No (n = 1,353)	p Value
Assigned to CABG arm	146 (42.2)	801 (51.5)	0.001	134 (43.2)	677 (50.0)	0.030
Age, yrs	64.9 ± 9.7	62.7 ± 8.9	<0.001	62.2 ± 9.1	63.1 ± 8.9	0.107
Age groups, yrs			<0.001			0.214
<50	22 (6.4)	122 (7.9)		28 (9.0)	98 (7.2)	
50–59	80 (23.1)	466 (30.0)		97 (31.3)	383 (28.3)	
60–69	124 (35.8)	617 (39.7)		108 (34.8)	555 (41.0)	
≥70	120 (34.7)	349 (22.5)		77 (24.8)	317 (23.4)	
Male	243 (70.2)	1,113 (71.6)	0.604	201 (64.8)	999 (73.8)	0.001
White	269 (77.7)	1,182 (76.1)	0.517	247 (79.7)	1,024 (75.7)	0.135
BMI, kg/m^2	29.5 ± 5.7	29.8 ± 5.0	0.306	30.0 ± 5.7	29.7 ± 5.2	0.347
History of smoking	65 (18.8)	233 (15.0)	0.027	51 (16.5)	207 (15.3)	0.436
Prior myocardial infarction	106 (30.6)	381 (24.5)	0.018	70 (22.6)	345 (25.5)	0.284
Prior cerebrovascular event	24 (6.9)	41 (2.6)	<0.001	12 (3.9)	39 (2.9)	0.362
History of peripheral vascular disease	35 (12.5)	161 (9.9)	0.201	27 (8.7)	141 (10.4)	0.367
Chronic lung disease	21 (6.1)	62 (4.0)	0.086	10 (3.2)	55 (4.1)	0.491
Recent acute coronary syndrome	121 (35.0)	462 (29.7)	0.055	84 (27.1)	422 (31.2)	0.157
3-vessel disease	298 (87.1)	1275 (82.5)	0.038	254 (81.9)	1121 (83.4)	0.532
On insulin	148 (42.8)	467 (30.1)	<0.001	109 (35.2)	410 (30.3)	0.095
LVEF, %	55.8 ± 13.1	59.0 ± 11.2	<0.001	59.9 ± 11.4	58.7 ± 11.3	0.090
Hemoglobin, g/dl	13.3 ± 1.9	13.8 ± 1.6	<0.001	13.5 ± 1.7	13.8 ± 1.6	0.006
Hemoglobin A1C <7 g/dl	99 (31.4)	531 (37.0)	0.060	101 (36.7)	465 (36.7)	0.986
eGFR MDRD, ml/min/1.73 m^2	63.6 ± 19.8	70.9 ± 17.4	<0.001	69.1 ± 17.6	70.6 ± 17.8	0.176
EuroSCORE	3.4 ± 3.0	2.5 ± 2.3	<0.001	2.5 ± 2.1	2.6 ± 2.3	0.606
SYNTAX score			0.006			0.399
Mean	27.3 ± 8.6	25.9 ± 8.6		25.8 ± 8.4	26.3 ± 8.6	
Median	26.0 (21.0–32.0)	26.0 (19.8–31.0)		26.0 (19.0–31.0)	26.0 (20.0–31.5)	
SYNTAX score >22	238 (68.8)	987 (63.5)	0.063	198 (63.9)	880 (65.0)	0.697
Number of antianginal medications	1.5 ± 0.9	1.5 ± 0.9	0.489	1.5 ± 0.9	1.4 ± 0.9	0.825
Angina frequency			0.177			<0.001
Daily/weekly	96 (34.5)	593 (37.0)		156 (50.8)	446 (33.1)	
Monthly	127 (45.7)	639 (39.9)		116 (37.8)	556 (41.2)	
No angina	55 (19.8)	369 (23.0)		35 (11.4)	346 (25.7)	
SAQ angina frequency	72.0 ± 23.8	71.0 ± 25.1	0.491	62.3 ± 26.2	73.4 ± 24.2	<0.001

Values are n (%), mean ± SD, or median (interquartile range). *Data on angina frequency at 1 year was missing in 237 patients.

BMI = body mass index; CABG = coronary artery bypass grafting; eGFR = estimated glomerular filtration rate; LVEF = left ventricular ejection fraction; MACE = major acute cardiovascular events; MDRD = Modification of Diet in Renal Disease Study; SAQ = Seattle Angina Questionnaire.

t-tests for continuous variables and chi-square tests for categorical variables. We developed separate multivariable models for MACE at 5 years (Cox proportional hazards regression) and for having angina at 1 year (logistic regression). Patients with missing angina frequency scores at 1 year (n = 237) were excluded from the angina model. As the intent of the models was to guide treatment after the performance of coronary angiography, but before revascularization, only variables available at the time of intended decision-making were included. Candidate variables were selected a priori based upon published data and clinical experience, and interactions between each candidate variable and treatment were explored. Candidate variables for the MACE model included: age, sex, race, body mass index (BMI), smoking history, history of MI, history of stroke, history of PCI, chronic obstructive pulmonary disease, peripheral vascular disease, insulin use, reason for revascularization (acute coronary syndrome [ACS] vs. stable CAD), estimated glomerular filtration rate, hemoglobin, left ventricular ejection fraction (LVEF), and SYNTAX score (categorized as ≤22 vs. >22 [15]). Candidate variables for the angina model included the same variables, in addition to baseline SAQ AF categories of daily/weekly (SAQ AF 0 to 60), monthly (SAQ AF 61 to 99), and no angina (SAQ AF = 100), and the number of antianginal medications at baseline. Both the categorization of the SYNTAX score and SAQ AF scale were designed to support clinical use of the models, as it was felt that clinicians could estimate these categories even if formal assessments were not

FIGURE 1 Risk Prediction Model for MACE At 5 Years in Patients With Diabetes and Multivessel Disease From FREEDOM Trial



Hazard ratios (HRs) are presented separately for percutaneous coronary intervention versus coronary artery bypass grafting (CABG) for variables with significant interaction with revascularization strategy. CI = confidence interval; eGFR = estimated glomerular filtration rate; FREEDOM = Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease; LVEF = left ventricular ejection fraction; MACE = major adverse cardiovascular events; MI = myocardial infarction; PCI = percutaneous coronary intervention.

performed. Spline terms were considered for all continuous variables to test for linearity. The spline was significant for the association of age with MACE, and so age was categorized as <50, 50 to 59, 60 to 69, and ≥70. To improve clinical applicability, backward variable selection was used with a p value of <0.2 for retention of covariates. Discrimination of the models was assessed using C-statistics, and calibration was tested by plotting deciles of predicted risk against observed event rates and comparing the slope of the regression line as well as the intercept for significant deviations between 1 and 0, respectively.

Both models were internally validated using bootstrap resampling with 500 replications (16,17). For each step of resampling, the model was refit using the method described in the previous text, and model discrimination and calibration were assessed on the bootstrapped data and then validated on the original dataset. The difference in performance between the 2 datasets was calculated and averaged over the 500 replications to calculate optimism-adjusted C-statistics.

MODEL EXTERNAL VALIDATION. After the MACE prediction model was built, its performance, in terms of discrimination and calibration, was tested on a cohort of patients from British Columbia, Canada. A detailed description of the cohort and outcome assessments has been previously published (6). In brief, the cohort was derived from a population-based registry that collects detailed clinical and procedural data on all adults undergoing cardiac catheterization, PCI, or CABG in British Columbia. The validation cohort included all British Columbia patients who were ≥20 years of age with DM and angiographically confirmed multivessel CAD (stenosis of >70% in 2 or more major epicardial vessels, excluding the left main coronary artery), who underwent either PCI or isolated CABG between October 2007 and January 2014 in British Columbia. Exclusion criteria were then applied to create a cohort that mimics the FREEDOM trial cohort. The components of the MACE outcome were determined by International Classification of Disease-Tenth Revision diagnosis codes. The patients were followed from the time of procedure to MACE, end of 5-year follow-up, or end of study, March 2014, whichever came first. The external validation was performed overall and separately on patients with stable CAD and ACS.

DEMONSTRATING THE HETEROGENEITY OF BENEFIT OF REVASCULARIZATION STRATEGY. To understand the

TABLE 2 Predicting Risk of 5-Year MACE Model (The Reduced Model)

	Regression Coefficient	Standard Error	p Value
Revascularization strategy (PCI)	0.01860	0.17253	0.9142
Age (50–59 yrs)*	−0.14618	0.24227	0.5463
Age (60–69 yrs)*	−0.02349	0.23427	0.9201
Age (≥70 yrs)*	0.39064	0.23720	0.0996
BMI (+1 unit)	−0.01665	0.01034	0.1073
History of smoking	0.08001	0.16811	0.6341
History of myocardial infarction	0.28813	0.11889	0.0154
History of stroke	0.61882	0.21482	0.0040
On insulin	0.43909	0.11114	<0.0001
eGFR (+10 ml/min per 1.73 m^2)	−0.1708	0.00298	<0.0001
LVEF (<50%)	0.47982	0.12478	0.0001
Revascularization with PCI × smoking	0.44995	0.22391	0.0445

This table contains the estimated Cox regression coefficients for the significant variables that are entered into the 5-year MACE model. The 5-year individualized MACE predicted risk can be calculated as follows (substitute 1 or 0 for presence or absence of any categorical variable: age category, smoking, history of MI, history of stroke, on insulin and LVEF <50%. For the variable "treatment" substitute 1 for PCI and 0 for CABG. For all continuous variables [BMI and eGFR] plug the actual value in the equation) = 1 − 0.48903-exp(0.01860 × treatment − 0.14618 × (if 50 ≤ age ≤59) −0.02349 × (if 60≤ age ≤69) + 0.39064 × (if age ≥70) −0.01665 × BMI + 0.08001 × (if history of smoking) +0.28813 × (if history of MI) + 0.61882 × (if history of stroke) + 0.43909 × (if on insulin) − 0.01708 × eGFR + 0.47982 × (if LVEF <50%) + 0.44995 × treatment × (if history of smoking). *Reference group for age is <50 years.

PCI = percutaneous coronary intervention; other abbreviations as in Table 1.

degree of variability in patients' predicted MACE and angina outcomes with PCI versus CABG, we calculated (on the basis of our model) each patient's individualized predicted probability of MACE and angina twice, first assuming treatment with multivessel PCI and second assuming treatment with CABG. Through bootstrap analyses, we assessed whether these personalized predictions for CABG were higher or lower than the personalized predictions for PCI (for that individual patients) with 95% confidence ($p < 0.05$).

All statistical analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina) and R version 3.3.1 (R Foundation, Vienna, Austria) (18).

RESULTS

PATIENT CHARACTERISTICS. There were 1,900 patients with diabetes and multivessel CAD who were enrolled in FREEDOM and randomized to CABG (n = 947) or PCI (n = 953), all of whom were included in the MACE models. Comparisons of patient characteristics for patients in the angina analytic cohort compared with those alive but with missing data are shown in Online Table 1. Among patients in the analytic cohorts, 346 of 1,900 (18.2%) experienced a MACE in the 5 years after randomization (CABG vs. PCI: 15.4% vs. 20.9%) and 310 (16.3%) reported angina at 1 year (CABG vs. PCI: 14.1% vs. 18.4%). Comparisons of patients with versus without MACE and with versus without angina are shown in Table 1. Patients with MACE were more likely to be older, have a history of smoking, have had a prior MI or cerebrovascular event, have 3-vessel disease, be on insulin, and to have a lower LVEF, lower hemoglobin, lower estimated glomerular filtration rate, higher EuroSCORE, and higher SYNTAX scores. Patients who reported angina at 1 year were more likely to be women, have lower hemoglobin, and have angina at baseline (Table 1).

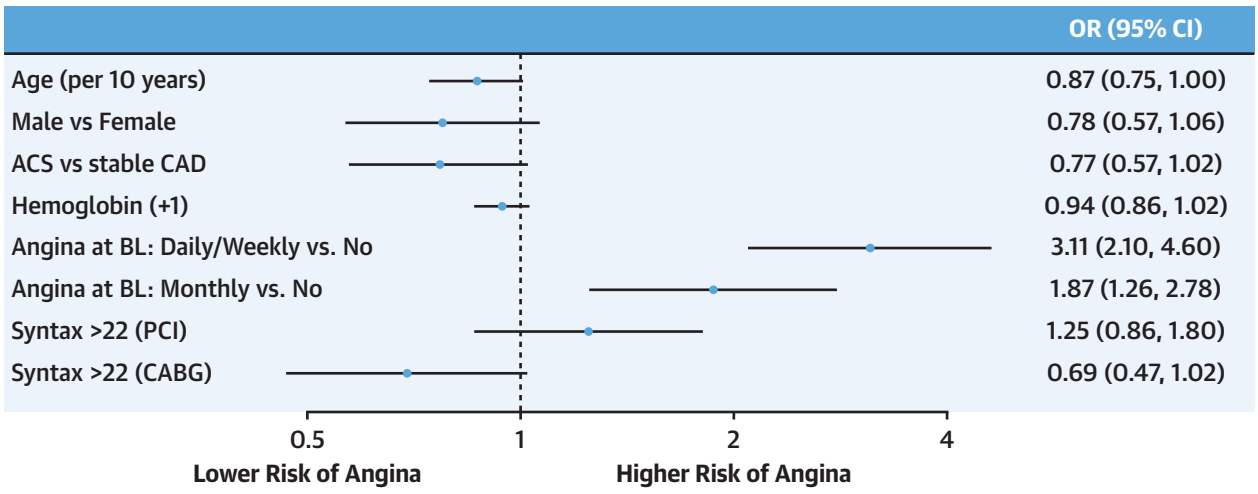
RISK MODEL FOR MACE OVER 5 YEARS. The final MACE model included 8 covariates and a treatment interaction with a history of smoking (p for interaction = 0.04) (Figure 1, Table 2), where patients with a history of smoking had a lower risk of MACE with CABG compared with PCI. The C-statistic was 0.67 in the derivation cohort, with good internal validation (bootstrap C-statistic of 0.65) and excellent calibration of predicted and observed risk (Online Figure 1). The predicted risk, by deciles, ranged from 9% to 51% over 5 years.

EXTERNAL VALIDATION OF THE MACE MODEL. The external validation cohort included 1,358 patients with stable CAD and 2,242 patients with stabilized ACS (Online Table 2) over a median follow-up of 3.48 years (interquartile range: 1.92 to 4.98 years). MACE occurred in 19.4% of the stable CAD cohort and in 33.8% of the ACS cohort. In the stable CAD cohort, the MACE model showed moderate discrimination (C-statistic 0.65) and good calibration, with an intercept of 0.04 ($p = 0.69$) and a slope of 0.60 ($R^2 = 0.90$) with slightly higher predicted than observed rates in the highest decile of risk in the stable CAD cohort. In the ACS cohort, the MACE model also showed moderate discrimination (C-statistic 0.68) and good calibration, with an intercept of 0.07 ($p = 0.90$) and a slope of 0.83 ($R^2 = 0.92$) with slightly lower predicted than observed rates in the stabilized ACS cohort (Online Figure 2).

RISK MODEL FOR ANGINA AT 1 YEAR. The final angina model included 6 variables and a treatment interaction with SYNTAX score (p for interaction = 0.02) (Figure 2, Table 3), such that patients with intermediate/high SYNTAX scores had less angina with CABG versus PCI. The discrimination of the angina model was 0.67 in the development cohort, which reduced to 0.64 after optimism correction with internal validation. The model had excellent calibration with a predicted angina, across deciles, of 7% to 33% (Online Figure 3).

DESCRIBING THE HETEROGENEITY OF TREATMENT EFFECT. As described above in the statistical methods, we calculated (on the basis of our model)

FIGURE 2 Risk Prediction Model for Angina at 1 Year in Patients With Diabetes and Multivessel Disease From FREEDOM Trial



Odds ratios (ORs) are presented separately for percutaneous coronary intervention versus coronary artery bypass grafting for variables with significant interaction with revascularization strategy. ACS = acute coronary syndrome; BL = baseline; CAD = coronary artery disease; CI = confidence interval; other abbreviations as in Figure 1.

each patient's individualized predicted probability of MACE and angina twice, first assuming treatment with multivessel PCI and second assuming treatment with CABG. Approximately one-half of patients (54.5%) would be expected to have a lower risk of MACE with CABG and 45.5% would be expected to have statistically similar MACE risk with CABG and PCI. No patients were predicted to have lower MACE with PCI than with CABG. We also note, based on the interaction with history of smoking, that all patients who had a history of smoking are expected to have a lower risk of MACE with CABG versus PCI. Similarly, 35% of patients would be expected to have a similar angina relief with CABG and PCI, and the rest of the patients would be expected to have better angina relief with CABG. We also note, based on the interaction with the SYNTAX score, that all patients who had SYNTAX score >22 are expected to have angina relief with CABG versus PCI and all patients with SYNTAX score ≤22 are expected to have a similar angina relief with CABG and PCI.

Figure 3 displays theoretical patient scenarios for which these models could be used for shared decision-making. In example 1, a 55-year-old diabetic patient (not on insulin) with no prior medical history with normal LVEF and BMI of 24 kg/m² who presented with weekly angina would have a predicted 5-year MACE of 5.1% (95% confidence interval [CI]: 1.9% to 13%) with CABG versus 5.2% (95% CI: 1.8% to 14%) with PCI and a 1-year predicted risk of angina of 25.0% (95% CI: 18% to 34%) with CABG versus 24.0% (95% CI: 17% to 32%) with PCI. In contrast, a 55-year-old patient with insulin-dependent diabetes and a history of prior stroke, who smoked, had a prior myocardial infarction with depressed LVEF of 20% and a BMI of 35 kg/m², and who presented with weekly angina would have a predicted 5-year MACE of 25% (95% CI: 8% to 68%) with CABG versus 38% (95% CI: 12% to 83%) with PCI and a 1-year predicted

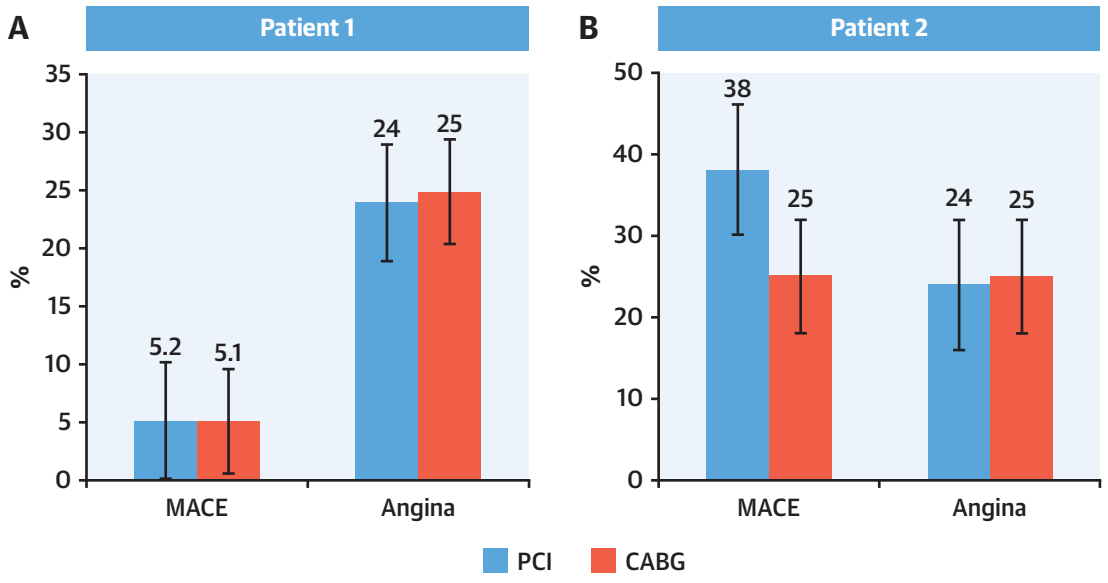
TABLE 3 Predicting Risk of 1-Year Angina Model (The Reduced Model)

	Regression Coefficient	Standard Error	p Value
Intercept	−0.1099	0.8079	0.8918
Revascularization strategy (PCI)	−0.07646	0.2149	0.7220
Age	−0.01316	0.007276	0.0707
Male	−0.2904	0.1458	0.0466
Presentation as acute coronary syndrome	−0.2818	0.1442	0.0509
Hemoglobin (+1 g/dl)	−0.06585	0.04219	0.1188
Daily/weekly angina at baseline*	1.1275	0.1972	<.0001
Monthly angina at baseline*	0.6244	0.2009	0.0019
SYNTAX score (>22)	−0.3790	0.1963	0.0536
Revascularization with PCI × SYNTAX (>22)	0.5900	0.2700	0.0290

This table contains the estimated logistic regression coefficients for the significant variables that are entered into the 1-yr angina model. The 1-yr individualized angina predicted risk can be calculated as follows (substitute 1 or 0 for presence or absence of any categorical variable: presenting as ACS, history of MI, history of peripheral vascular disease, male and angina at baseline. For the variable "treatment" substitute 1 for PCI and 0 for CABG. For all continuous variables [BMI, eGFR, LVEF, hemoglobin and age] plug the actual value in the equation) = 1/(1 + exp[− (−1.1504 − 0.02040 × treatment × BMI + 0.01612 × BMI − 0.00727 × treatment × eGFR + 0.002129 × eGFR + 0.2870 × treatment × presenting as ACS − 0.2912 × treatment × history of MI + 0.05326 × history of MI − 0.5213 × treatment × history of peripheral vascular disease + 0.08552 × history of peripheral vascular disease + 0.006867 × LVEF − 0.07286 × hemoglobin − 0.01575 × age − 0.4273 × presenting as ACS + 1.4594 × treatment − 0.2648 × Male + 0.8988 × angina at baseline)]). *Reference group for angina is no angina.

Abbreviations as in Tables 1 and 2.

FIGURE 3 Potential Model Output for Shared Decision-Making



This bar graph figure shows theoretical patient scenarios **(A and B)** for which our models can provide individualized predictions (along with 95% CI) for 5-year major adverse cardiovascular events (MACE) and 1-year angina for percutaneous coronary intervention (PCI) versus coronary artery bypass grafting (CABG). Please see the text for actual numbers.

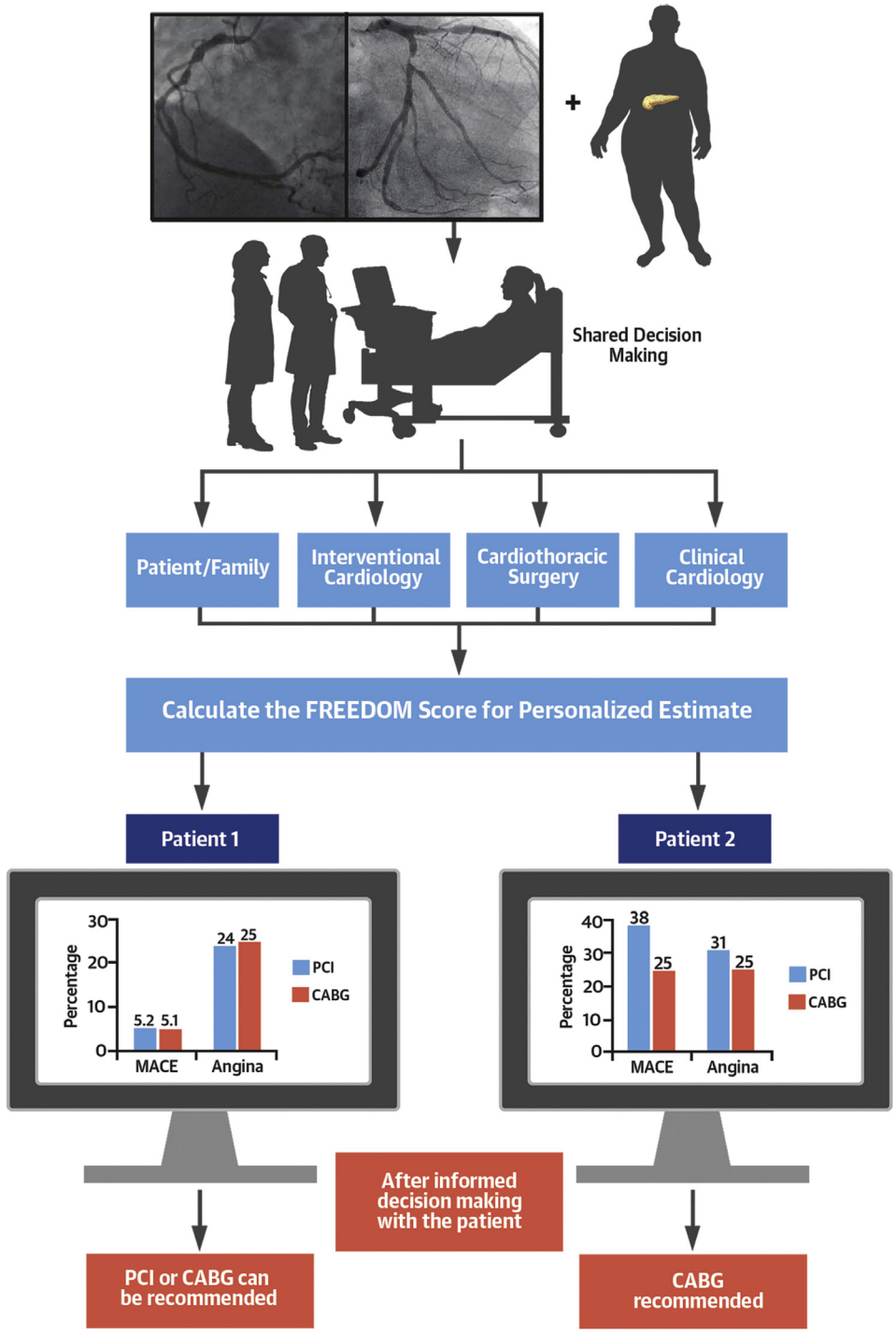
risk of angina of 25.0% (95% CI: 18% to 34%) with CABG versus 24.0% (95% CI: 17% to 32%) with PCI.

DISCUSSION

The promise of precision medicine is to illuminate how a patient would be expected to fare with one treatment versus another. Although clinical trials, such as FREEDOM, provide the highest-quality evidence of the relative efficacy of alternative treatments, they report the mean effects of treatments across populations of randomized patients. Because no patient is "average," these results can be difficult to apply to individual patients in routine clinical practice. Moreover, treatment options are usually presented by the treating physician, who may overestimate or underestimate the benefits or harms of a particular treatment, depending on their specialty, experience, and background. To overcome this challenge, personalized risk tools can be used to estimate an individual patient's outcomes with different treatments. The case of PCI versus CABG for patients with multivessel disease and diabetes provides an ideal setting for this approach, as there are trade-offs in terms of periprocedural risks, length of recovery, and long-term outcomes. In this study, we derived and validated risk models for long-term MACE and angina after CABG and PCI, based on data from the FREEDOM trial, that could be used to support patient decision-making (**Central Illustration**). Furthermore, in a separate cohort of consecutive patients from British Columbia, we found the MACE model to perform exceedingly similarly to what was observed in the FREEDOM trial, even among patients presenting with an ACS. We found that patients with a history of smoking did better with CABG, with respect to long-term MACE outcomes. We also found that patients with higher SYNTAX scores were more likely to be angina-free at 1 year after CABG, although SYNTAX score did differentiate MACE rates between CABG and PCI. While no patients were predicted to have better outcomes (either MACE or angina) with PCI, there were a number of patients with statistically similar outcomes with CABG and PCI, in whom more discretion in the use of PCI might be reasonable after an informed discussion with patients.

PRIOR PUBLISHED DATA. Although several randomized clinical trials (19-24) have addressed the best revascularization strategy for patients with multivessel CAD, only a few risk tools have been created to attempt to personalize treatment choices. One such tool is the SYNTAX II score, which estimates long-term mortality for patients with complex CAD, but neither MACE nor angina outcomes were included in that model (25). While there were a number of similarities between the 2 risk scores including some

CENTRAL ILLUSTRATION **Proposed Shared Decision-Making Algorithm for Patients With Multivessel Coronary Artery Disease and Diabetes Utilizing the FREEDOM Score**



Qintar, M. et al. J Am Coll Cardiol. 2019;74(16):2074–84.

Utilizing our innovative FREEDOM score, a heart-team approach can be undertaken to engage patients and their physicians to make an informed decision about the best treatment strategy for their coronary artery disease. CABG = coronary artery bypass grafting; PCI = percutaneous coronary intervention.

similar predictors, the SYNTAX II score estimated that 29% of patients with low SYNTAX score would have statistically better long-term mortality risk with PCI, which was not found in the diabetic patients enrolled in FREEDOM. Furthermore, CABG was superior to PCI for patients with intermediate/high SYNTAX scores in the SYNTAX trial but did not seem to be associated with better MACE outcomes in FREEDOM, although it was better for relieving angina at 1 year.

CLINICAL IMPLICATIONS. Although the overwhelming evidence favors CABG in patients with diabetes and multivessel disease, PCI still remains a common revascularization strategy in the real world. Thus, we believe that our models can help disseminate best treatment recommendations by showing both physicians and patients the expected benefits compared with multivessel PCI. Clinicians can use an online calculator (26), and personalized estimates based on our models will be calculated. However, numerous potential reasons exist for why patients with diabetes and multivessel CAD may prefer being treated with PCI, despite guideline recommendations and clear clinical trial results. To help objectify the discussion, our tool can transparently show the estimated risks and benefits of both PCI and CABG so that a more informed discussion can occur. We believe that using such tools can alleviate some of the barriers that exist in routine clinical care and can lead to more evidence-based, patient-centered care. For example, in many patients, the predicted risks of poor outcomes with CABG were substantially lower than with PCI, which could alter the strength of the recommendation to proceed with CABG, despite the longer recovery. In addition, in a minority of cases where the predicted risks are similar with CABG or PCI, there may be more comfort in allowing a choice of multivessel PCI despite the overall results of FREEDOM showing superiority of CABG. The careful investigation of using these risk models in routine clinical care is needed to understand its impact on adoption of clinical trial results and patient outcomes.

Although the discrimination of our models may seem modest, we would argue that they can be clinically useful. First, Kent et al. (27) and Hayward et al. (28) have argued that a C-statistic >0.60 can help improve clinical trials, and the use of risk models clearly enable the results of the FREEDOM trial to be applied to individual patients. In addition, the ranges of risk that were estimated across the population were large and clinically important when trying to communicate such complex information to patients. Finally, previous work from our group has shown that the prospective application of a bleeding risk model for PCI with a similar C-statistic (0.72) resulted in a 44% reduction in bleeding (29,30). To further define the value of these risk models, they should be prospectively studied in routine clinical care to understand their impact on shared decision-making and clinical outcomes.

STUDY LIMITATIONS. First, as this is a post hoc analysis from a randomized clinical trial, our models may not work as well in more general populations. However, the validation of the MACE model in an external cohort somewhat mitigates this concern. Second, we modeled our MACE prediction tool at 5 years and angina at 1 year. It is possible that CABG might confer more (or less) benefit on symptom control over PCI over a longer time period. Third, the stents used in FREEDOM were first-generation DES, and it is possible that the use of newer stents might provide better outcomes. However, the primary benefit of newer DES are avoidance of repeat procedures, which was not part of our MACE outcome (31-33). Finally, although FREEDOM did not have narrow inclusion criteria and we externally validated the models in a real-world registry, clinicians still face the conundrum of applying clinical trial results to patients who were not eligible for randomization (e.g., prohibitive surgical risk) and the use of an evidence-based model does not exacerbate this problem.

CONCLUSIONS

Using data from a large randomized clinical trial of patients with diabetes and multivessel CAD, we created personalized risk prediction tools that can estimate long-term MACE and angina after revascularization. We found that CABG was the preferred strategy in the majority of patients, especially among those with a history of smoking. Although PCI was never the preferred revascularization strategy, 45% of patients were expected to have similar risks of poor outcomes with CABG or PCI, and patient preferences may play a larger role in the treatment decision among these patients. This tool should be prospectively tested at the point of care to see whether or not it can improve the process of shared medical decision-making and increase the use of CABG in patients most expected to benefit from this strategy.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE AND PATIENT CARE: We created personalized risk prediction tools that can estimate long-term MACE and angina outcomes after revascularization in diabetic patients with multivessel disease. CABG was the preferred strategy in the majority of patients; however, 45% of patients were expected to have similar risks of poor outcomes with CABG or PCI, and patient preferences may play a larger role in the treatment decision among these patients.

TRANSLATIONAL OUTLOOK: This tool should be prospectively tested at the point of care to see whether or not it can improve the process of shared medical decision-making and increase the use of CABG in patients most expected to benefit from this strategy.

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KEY WORDS coronary artery bypass graft, coronary artery disease, diabetes, multivessel disease, percutaneous coronary intervention, personalized risk estimate, shared decision making

APPENDIX For supplemental tables and figures, please see the online version of this paper.