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ORIGINAL INVESTIGATIONS

Medical Treatment and Revascularization Options in Patients With Type 2 Diabetes and Coronary Disease

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ABSTRACT

BACKGROUND There are scant outcomes data in patients with type 2 diabetes and stable coronary artery disease (CAD) stratified by detailed angiographic burden of CAD or left ventricular ejection fraction (LVEF).

OBJECTIVES This study determined the effect of optimal medical therapy (OMT), with or without percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), on long-term outcomes with respect to LVEF and number of diseased vessels, including proximal left anterior descending artery involvement.

METHODS A patient-level pooled analysis was undertaken in 3 federally-funded trials. The primary endpoint was the composite of death, myocardial infarction (MI), or stroke, adjusted for trial and randomization strategy.

RESULTS Among 5,034 subjects, 15% had LVEF <50%, 77% had multivessel CAD, and 28% had proximal left anterior descending artery involvement. During a median 4.5-year follow-up, CABG + OMT was superior to PCI + OMT for the primary endpoint (hazard ratio [HR]: 0.71; 95% confidence interval [CI]: 0.59 to 0.85; p = 0.0002), death (HR: 0.76; 95% CI: 0.60 to 0.96; p = 0.024), and MI (HR: 0.50; 95% CI: 0.38 to 0.67; p = 0.0001), but not stroke (HR: 1.54; 95% CI: 0.96 to 2.48; p = 0.074). CABG + OMT was also superior to OMT alone for prevention of the primary endpoint (HR: 0.79; 95% CI: 0.64 to 0.97; p = 0.022) and MI (HR: 0.55; 95% CI: 0.41 to 0.74; p = 0.0001), and was superior to PCI + OMT for the primary endpoint in patients with 3-vessel CAD (HR: 0.72; 95% CI: 0.58 to 0.89; p = 0.002) and normal LVEF (HR: 0.71; 95% CI: 0.58 to 0.87; p = 0.0012). There were no significant differences in OMT versus PCI + OMT.

CONCLUSIONS CABG + OMT reduced the primary endpoint during long-term follow-up in patients with type 2 diabetes and stable CAD, supporting this as the preferred management strategy. (J Am Coll Cardiol 2016;68:985-95)

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

CAD = coronary artery disease

CI = confidence interval

HR = hazard ratio

LVEF = ejection fraction

MI = myocardial infarction

OMT = optimal medical therapy

PCI = percutaneous coronary intervention

pLAD = proximal left anterior descending

T2DM = type 2 diabetes mellitus

Cardiovascular disease is highly prevalent in patients with type 2 diabetes mellitus (T2DM), accounts for over one-half of all deaths in this population, generates approximately one-quarter of all referrals for coronary revascularization, and commonly creates management challenges because of the increasing frequency of T2DM (1–4). Although optimal medical therapy (OMT) is the foundation of treatment, and although the evidence base strongly favors the use of coronary artery bypass grafting (CABG) over percutaneous coronary intervention (PCI), particularly for multivessel disease, the decision to proceed initially with any of these options remains complex for several reasons, including highly variable patient characteristics, anatomic variations in CAD location, technical issues affecting PCI and CABG procedures, higher rates of suboptimal PCI results in patients with diabetes, increased need for repeat revascularization after PCI, concerns about perioperative stroke and mortality early after CABG, and diverse patient and physician preferences (5–7).

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Existing meta-analyses of outcomes in patients with T2DM address only multivessel CAD (8–21); of these, only 1 provides patient-level meta-analysis (19), whereas none evaluate the critical role of OMT as the foundation of any treatment strategy. This pooling project was undertaken to assess randomly-assigned treatment (OMT, PCI + OMT, and CABG + OMT), as represented by 3 landmark trials (22–24), with an initial emphasis on the possible effects on outcomes of underlying left ventricular ejection fraction (EF) and the full spectrum of angiographic CAD patterns, including the presence or absence of proximal left anterior descending (pLAD) disease.

METHODS

Patient-level data from 3 prospective, randomized, federally-funded clinical trials (BARI 2D [Bypass Angioplasty Revascularization Investigation 2 Diabetes], COURAGE [Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation], and FREEDOM [Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease]) that enrolled patients with stable CAD with T2DM between 1999 and 2010 were pooled. Key variables, common definitions, and coding for each covariate and outcome were established jointly. The coordinating center investigators extracted deidentified patient-level data from the respective databases, and the University of Pittsburgh Data Management and Biostatistics Core Laboratory merged these into a single, pooled, patient-level dataset.

The BARI 2D and FREEDOM trials included only patients with CAD and T2DM, whereas COURAGE enrolled a broader group of patients with CAD, of whom only those with baseline T2DM were included in this analysis. Patients in the COURAGE trial were randomly assigned to OMT or PCI + OMT; patients in the FREEDOM trial were randomly assigned to PCI + OMT or CABG + OMT. In the BARI 2D trial, patients were first selected for PCI or CABG eligibility on the basis of physician judgment and coronary anatomy, and were then randomly assigned in the PCI stratum to OMT or PCI + OMT, and in the CABG stratum to OMT or CABG + OMT. As a result, the 2 strata in BARI 2D were considered separate clinical trials.

The primary outcome was the composite of death, myocardial infarction (MI), or stroke. The outcome definitions were those established for each trial. MI was centrally adjudicated in each trial (Online Appendix), as was stroke in the BARI 2D and FREEDOM trials, whereas site-reported stroke events were not centrally adjudicated in COURAGE. All trials had core laboratories that assessed baseline angiographic CAD. When core angiographic data were missing (n = 18), site angiographic data were used when available (n = 15). When the core laboratory determined that there was no lesion exceeding the 50% stenosis threshold (n = 169), the vessel with the greatest stenosis by core laboratory assessment was designated as the single vessel with disease.

Baseline variables were compared across the trials and were assigned treatment groups using Kruskal-Wallis statistics for continuous variables and chi-square statistics for categorical variables. All outcome comparisons were conducted according to the intention-to-treat principle, and time-to-event

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outcomes were censored at 5 years. The unadjusted event rates by assigned treatment strategy were on the basis of Kaplan-Meier estimation. Trial-adjusted estimates of treatment effects were on the basis of Cox proportional hazards regression, representing the ratio of hazards of an event occurring averaged over the 5-year period. Each of the 4 trial cohorts (COURAGE, FREEDOM, BARI 2D PCI stratum, and BARI 2D CABG stratum) had a random treatment assignment, and each had a unique patient profile and corresponding level of risk. By adjusting for trial, we harnessed the random treatment assignment within each trial to create a multivariable model that produced a risk estimate for each of the 3 treatment strategies, accounting for the different patient profiles and risk levels among the 4 trials. Thus, the trial-adjusted multivariable model hazard ratios (HRs) could be used to validly compare the risk of an event for each pair of treatments. As a sensitivity analysis, we created a second set of multivariable models, using Cox regression, that adjusted for baseline factors that were clinically relevant or that differed among the trials (age, sex, geographic region, body mass index, presence of angina, and history of smoking, heart failure, hypertension, dyslipidemia, MI, renal dysfunction, prior revascularization procedure, and use of insulin). Adjusted survival curves by treatment strategy were created from these fully adjusted models.

HRs and 95% confidence intervals (CIs) are presented for the combined cohort and within subgroups on the basis of pre-defined angiographic factors (left ventricular ejection fraction [LVEF], number of diseased vessels, specific vessel involvement, and involvement of the pLAD segment). All patients were included in the overall analyses, but 3 patients who were missing angiographic information could not be included in the angiographic subgroup analyses. Similarly, patients with missing LVEF (n = 89) were included in the overall analyses, but not for subgroup stratification by LVEF (low LVEF defined as <50%). Tests for interaction were performed to assess for heterogeneity of treatment effects among subgroups. A p value of 0.05 was used to determine statistical significance for the treatment comparisons in the combined cohort. For subgroup analyses, p = 0.003 was used to account for the comparisons made in 17 overlapping subgroups.

RESULTS

There were 5,034 patients in the pooled analysis (COURAGE: n = 766; BARI 2D: n = 2,368; FREEDOM: n = 1,900). Clinical characteristics are summarized by treatment strategy in **Table 1** and by trial in Online Table 1. A total of 1,591 patients were randomized to OMT (16%), 2,118 to PCI + OMT (42%), and 1,325 to CABG + OMT (32%). There were 15% of patients with LVEF <50%, 28% with pLAD involvement, and 77% with 2- to 3-vessel CAD. Of the 2,051 (97%) patients who underwent the assigned PCI, 94% received stents and 58% received a drug-eluting stent. Of the 1,232 (93%) patients who underwent the assigned CABG, 94% had an internal mammary artery graft. There were 1,013 patients with death, MI, or stroke events: 535 patient deaths, 525 MIs, and 136 strokes (median 4.5-year follow-up). Online Table 2 shows the unadjusted Kaplan-Meier 5-year event rates and patient counts stratified by treatment and trial.

Figure 1 shows the unadjusted survival curves for the composite outcome and components. **Table 2** summarizes the unadjusted HR, the trial-adjusted HR (primary analysis), and the multivariable-adjusted HR (sensitivity analysis). CABG + OMT was superior to PCI + OMT for the primary composite endpoint (HR: 0.71; 95% CI: 0.59 to 0.85; p = 0.0002) and for the endpoints of death (HR: 0.76; 95% CI: 0.60 to 0.96; p = 0.024) and MI (HR: 0.50; 95% CI: 0.38 to 0.67; p = 0.0001), but not stroke (HR: 1.54; 95% CI: 0.96 to 2.48; p = 0.074). CABG + OMT was also superior to OMT alone for prevention of the primary endpoint (HR: 0.79; 95% CI: 0.64 to 0.97; p = 0.022) and MI (HR: 0.55; 95% CI: 0.41 to 0.74; p = 0.0001). All analyses comparing OMT and PCI + OMT were nonsignificant (**Central Illustration**). The multivariable-adjusted sensitivity analysis yielded concordant results. Cox-adjusted survival curves are shown in Online Figure 1.

Figure 2 shows no significant heterogeneity among the subgroups on the basis of the number of diseased vessels, pLAD, and LVEF for the risk of the composite endpoint. Using the corrected p = 0.003 threshold for subgroups, all comparisons of PCI + OMT with OMT and of CABG + OMT with OMT were statistically nonsignificant. CABG + OMT significantly reduced the risk of the primary endpoint compared with PCI + OMT for the subgroup with 3-vessel disease (HR: 0.72; 95% CI: 0.58 to 0.89; p = 0.002), and the subgroup with normal LVEF (HR: 0.71; 95% CI: 0.58 to 0.87; p = 0.0012). CABG + OMT was not statistically different from PCI + OMT for patients with 1-vessel (HR: 0.56; 95% CI: 0.23 to 1.41; p = 0.22) or 2-vessel (HR: 0.70; 95% CI: 0.47 to 1.06; p = 0.096) CAD; in the presence (HR: 0.71; 95% CI: 0.54 to 0.93; p = 0.014) or absence (HR: 0.71; 95% CI: 0.55 to 0.90; p = 0.0048) of pLAD; and for patients with low LVEF (HR: 0.69; 95% CI: 0.46 to 1.05; p = 0.09). Online Figure 2 shows the results for combinations of these variables.

TABLE 1 Patient Baseline Characteristics According to Treatment Strategy

	Total (N = 5,034)	1 OMT (n = 1,591)	2 PCI + OMT (n = 2,118)	3 CABG + OMT (n = 1,325)	p Value
Clinical trial					
BARI 2D PCI stratum	31.9 (1,605)	50.7 (807)	37.7 (798)	0.0 (0)	<0.0001
BARI 2D CABG stratum	15.2 (763)	24.2 (385)	0.0 (0)	28.5 (378)	
COURAGE	15.2 (766)	25.1 (399)	17.3 (367)	0.0 (0)	
FREEDOM	37.7 (1,900)	0.0 (0)	45.0 (953)	71.5 (947)	
Age, yrs	62.7 ± 9.1	62.4 ± 9.0	62.6 ± 9.1	63.0 ± 9.0	0.16
Female	26.9 (1,354)	26.2 (417)	26.0 (551)	29.1 (386)	0.10
Race					
White	74.0 (3,725)	73.1 (1,163)	73.7 (1,560)	75.6 (1,002)	<0.0001
Black	11.6 (586)	14.1 (225)	12.0 (255)	8.0 (106)	
Asian	5.7 (286)	3.6 (57)	6.0 (128)	7.6 (101)	
Other (non-White/Black/Asian)	8.7 (437)	9.2 (146)	8.3 (175)	8.8 (116)	
Hispanic ethnicity	20.0 (1,009)	11.1 (176)	21.2 (450)	28.9 (383)	<0.0001
Country					
United States	47.2 (2,375)	64.3 (1,023)	48.1 (1,018)	25.2 (334)	<0.0001
Canada	18.8 (946)	19.5 (310)	18.9 (400)	17.8 (236)	
Other (non-United States/Canada)	34.0 (1,713)	16.2 (258)	33.1 (700)	57.0 (755)	
BMI, kg/m^2	30.9 ± 5.7	31.7 ± 5.7	30.9 ± 5.9	29.9 ± 5.1	<0.0001
Smoking status					
Never	35.8 (1,797)	28.9 (458)	37.1 (785)	41.8 (554)	<0.0001
Former	48.9 (2,455)	56.6 (897)	46.7 (988)	43.1 (570)	
Current	15.4 (773)	14.6 (231)	16.2 (342)	15.1 (200)	
History of hypertension	83.0 (4,143)	81.8 (1,284)	82.7 (1,739)	84.9 (1,120)	0.073
History of dyslipidemia	76.9 (3,843)	71.5 (1,126)	77.0 (1,620)	83.2 (1,097)	<0.0001
History of heart failure	14.4 (724)	6.8 (107)	15.8 (333)	21.5 (284)	<0.0001
Prior myocardial infarction	30.3 (1,511)	33.3 (518)	29.9 (630)	27.5 (363)	0.0029
History of COPD	5.8 (292)	6.9 (110)	5.6 (118)	4.8 (64)	0.047
History of renal dysfunction	4.7 (238)	3.7 (58)	5.4 (114)	5.0 (66)	0.043
Prior PCI	11.9 (600)	18.9 (300)	12.2 (258)	3.2 (42)	<0.0001
Prior CABG	5.0 (252)	8.9 (142)	5.1 (109)	0.1 (1)	<0.0001
Angina					
No angina	15.5 (778)	18.8 (298)	14.5 (306)	13.1 (174)	<0.0001
Stable CCS I or atypical	27.6 (1,388)	33.7 (535)	27.6 (584)	20.3 (269)	
Stable CCS II	34.0 (1,708)	31.2 (495)	32.7 (691)	39.4 (522)	
Stable CCS III	15.5 (777)	9.3 (148)	17.3 (366)	19.9 (263)	
Stable CCS IV or unstable	7.5 (376)	7.1 (112)	7.9 (168)	7.3 (96)	
Diabetes treated with insulin	35.5 (1,783)	39.4 (626)	37.2 (787)	27.9 (370)	<0.0001
HbA_{1c},%	7.7 ± 1.7	7.7 ± 1.7	7.6 ± 1.7	7.7 ± 1.7	0.20
eGFR, ml/min/1.73 m^2	79.0 ± 32.3	78.2 ± 23.5	80.4 ± 34.8	77.6 ± 36.8	0.0043
Systolic blood pressure, mm Hg	133.0 ± 19.9	133.4 ± 20.1	132.7 ± 19.9	133.0 ± 19.8	0.69
Diastolic blood pressure, mm Hg	75.0 ± 11.2	74.9 ± 11.1	74.6 ± 11.2	75.8 ± 11.2	0.0065
Total cholesterol, mg/dl	177.3 ± 43.6	179.9 ± 43.9	173.2 ± 42.2	179.6 ± 45.9	<0.0001
LDL, mg/dl	97.8 ± 36.0	101.9 ± 36.4	95.6 ± 34.4	96.4 ± 37.8	<0.0001
HDL, mg/dl	40.0 ± 11.2	40.7 ± 11.3	39.7 ± 11.1	39.8 ± 11.2	0.015
Triglycerides, mg/dl	187.6 ± 212.2	194.6 ± 127.8	188.3 ± 291.1	177.6 ± 126.2	<0.0001
LVEF, %	60.5 ± 12.0	59.0 ± 11.5	60.7 ± 12.2	62.1 ± 12.0	<0.0001
LVEF <50%	15.0 (744)	16.4 (256)	15.3 (318)	13.0 (170)	0.035
RCA disease	74.0 (3,721)	62.9 (1,000)	73.3 (1,552)	88.3 (1,169)	<0.0001
LCX disease	70.5 (3,549)	57.5 (914)	70.9 (1,502)	85.6 (1,133)	<0.0001

Continued on the next page

Figure 3 shows exploratory analyses stratified by the specific angiographic location of CAD (i.e., right or left circumflex coronary, left anterior descending artery [but not pLAD], pLAD involvement, and combinations of these features) and with preserved LVEF. Using the corrected p = 0.003 threshold, none of the comparisons were statistically significant. The results pertaining to the

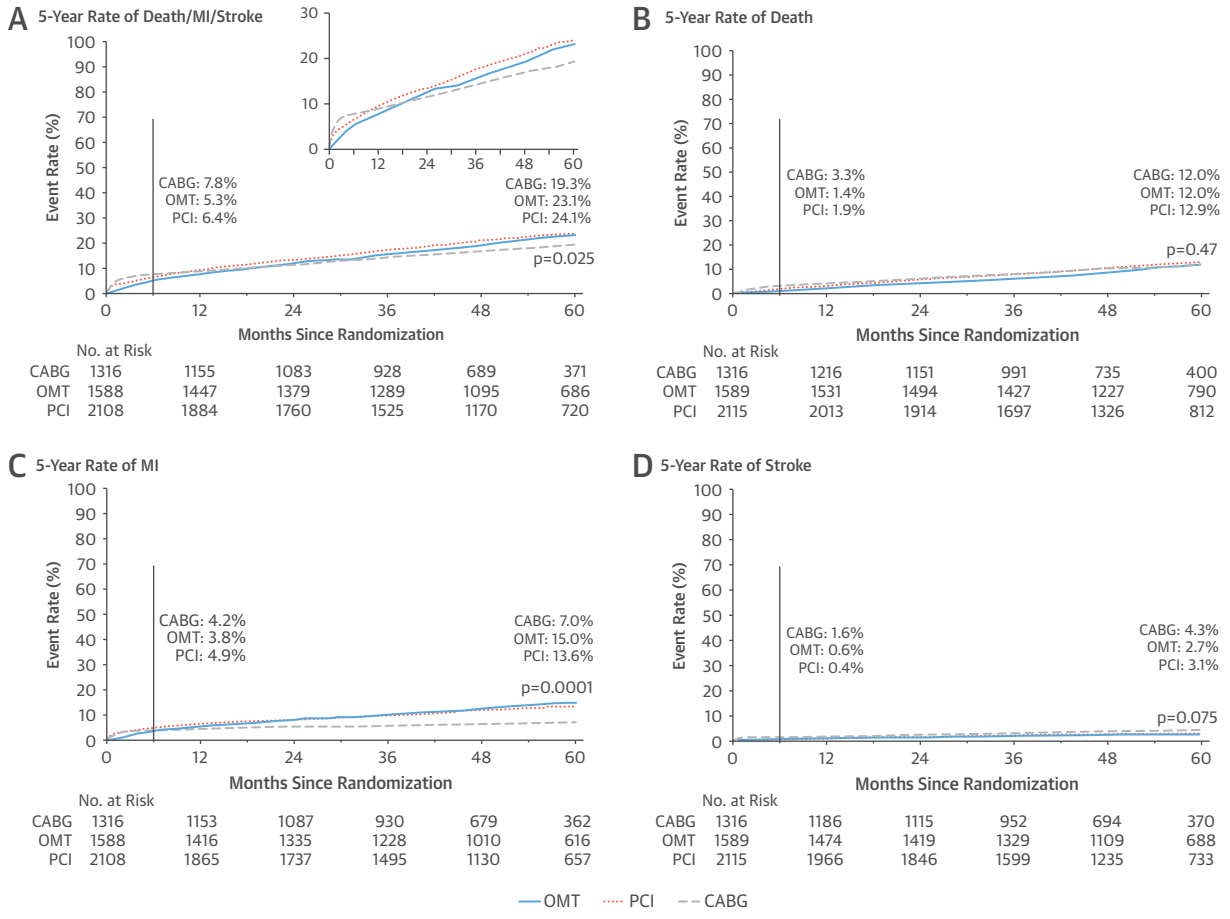
TABLE 1 Continued

	Total (N = 5,034)	1 OMT (n = 1,591)	2 PCI + OMT (n = 2,118)	3 CABG + OMT (n = 1,325)	p Value
Proximal LCX disease	26.4 (1,326)	9.2 (146)	30.4 (644)	40.5 (536)	<0.0001
LAD disease	80.6 (4,055)	69.2 (1,099)	80.4 (1,703)	94.6 (1,253)	<0.0001
Proximal LAD disease	28.1 (1,416)	16.3 (259)	29.7 (628)	40.0 (529)	<0.0001
Presence of total occlusion	36.3 (1,825)	38.4 (610)	31.9 (676)	40.7 (539)	<0.0001
Number of diseased vessels					
1	22.9 (1,150)	37.6 (597)	23.6 (499)	4.1 (54)	<0.0001
2	29.2 (1,468)	35.2 (560)	28.3 (599)	23.3 (309)	
3	48.0 (2,413)	27.2 (432)	48.2 (1,020)	72.6 (961)	

Values are % (n) or mean ± SD.

BARI 2D = Bypass Angioplasty Revascularization Investigation 2 Diabetes; BMI = body mass index; CABG = coronary artery bypass graft; CCS = Canadian Cardiovascular Society; COPD = chronic obstructive pulmonary disease; COURAGE = Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation; eGFR = estimated glomerular filtration rate; FREEDOM = Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease; HbA_{1c} = glycosylated hemoglobin; HDL = high-density lipoprotein; LAD = left anterior descending; LCX = left circumflex; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction; OMT = optimal medical therapy; PCI = percutaneous coronary intervention; RCA = right coronary artery.

FIGURE 1 Unadjusted Survival Curves



Curves are shown for the composite outcome **(A)**, death **(B)**, MI **(C)**, and stroke **(D)**. **Vertical line** is shown at 6 months with unadjusted event rates. CABG = coronary artery bypass graft; MI = myocardial infarction; OMT = optimal medical therapy; PCI = percutaneous coronary intervention.

TABLE 2 Unadjusted, Trial-Adjusted, and Multivariable-Adjusted HRs for the Composite Endpoint and the Individual Components From Cox Regression Models (N = 5,034)

	Unadjusted HR (95% CI)	Trial-Adjusted* HR (95% CI)	p Value	Multivariable-Adjusted* HR (95% CI)	p Value
Death/MI/stroke events (n = 1,013)					
PCI + OMT vs. OMT	1.08 (0.94-1.25)	1.11 (0.95-1.31)	0.18	1.14 (0.97-1.34)	0.11
CABG + OMT vs. OMT	0.87 (0.73-1.03)	0.79 (0.64-0.97)	0.022	0.81 (0.66-1.00)	0.044
CABG + OMT vs. PCI + OMT	0.80 (0.68-0.94)	0.71 (0.59-0.85)	0.0002	0.71 (0.59-0.86)	0.0003
Death events (n = 535)					
PCI + OMT vs. OMT	1.13 (0.93-1.38)	1.12 (0.90-1.41)	0.32	1.17 (0.93-1.46)	0.19
CABG + OMT vs. OMT	1.09 (0.86-1.36)	0.85 (0.65-1.12)	0.24	0.91 (0.69-1.19)	0.48
CABG + OMT vs. PCI + OMT	0.96 (0.78-1.19)	0.76 (0.60-0.96)	0.024	0.78 (0.61-0.99)	0.042
MI events (n = 525)					
PCI + OMT vs. OMT	0.94 (0.78-1.14)	1.09 (0.88-1.35)	0.41	1.11 (0.90-1.38)	0.34
CABG + OMT vs. OMT	0.51 (0.39-0.66)	0.55 (0.41-0.74)	0.0001	0.56 (0.41-0.75)	0.0001
CABG + OMT vs. PCI + OMT	0.54 (0.42-0.70)	0.50 (0.38-0.67)	0.0001	0.50 (0.38-0.67)	0.0001
Stroke events (n = 136)					
PCI + OMT vs. OMT	1.15 (0.76-1.74)	1.08 (0.68-1.70)	0.75	1.08 (0.68-1.70)	0.75
CABG + OMT vs. OMT	1.61 (1.04-2.49)	1.66 (0.93-2.96)	0.086	1.62 (0.91-2.89)	0.10
CABG + OMT vs. PCI + OMT	1.41 (0.95-2.09)	1.54 (0.96-2.48)	0.074	1.50 (0.93-2.42)	0.094

*Cox regression models adjusted by trial (COURAGE, FREEDOM, BARI 2D PCI stratum, BARI 2D CABG stratum) and by multiple variables as a sensitivity analysis (age, sex, geographic region, body mass index, and history of smoking, heart failure, hypertension, dyslipidemia, MI, renal dysfunction, prior revascularization procedure, presence of angina, and use of insulin). PCI + OMT, CABG + OMT and OMT are compared within the same model; OMT serves as the reference group for comparisons with PCI + OMT and with CABG + OMT; and PCI + OMT serves as the reference group for comparisons with CABG + OMT.

CI = confidence interval; HR = hazard ratio; MI = myocardial infarction; other abbreviations as in Table 1.

small subgroup with low LVEF are shown in Online Figure 3.

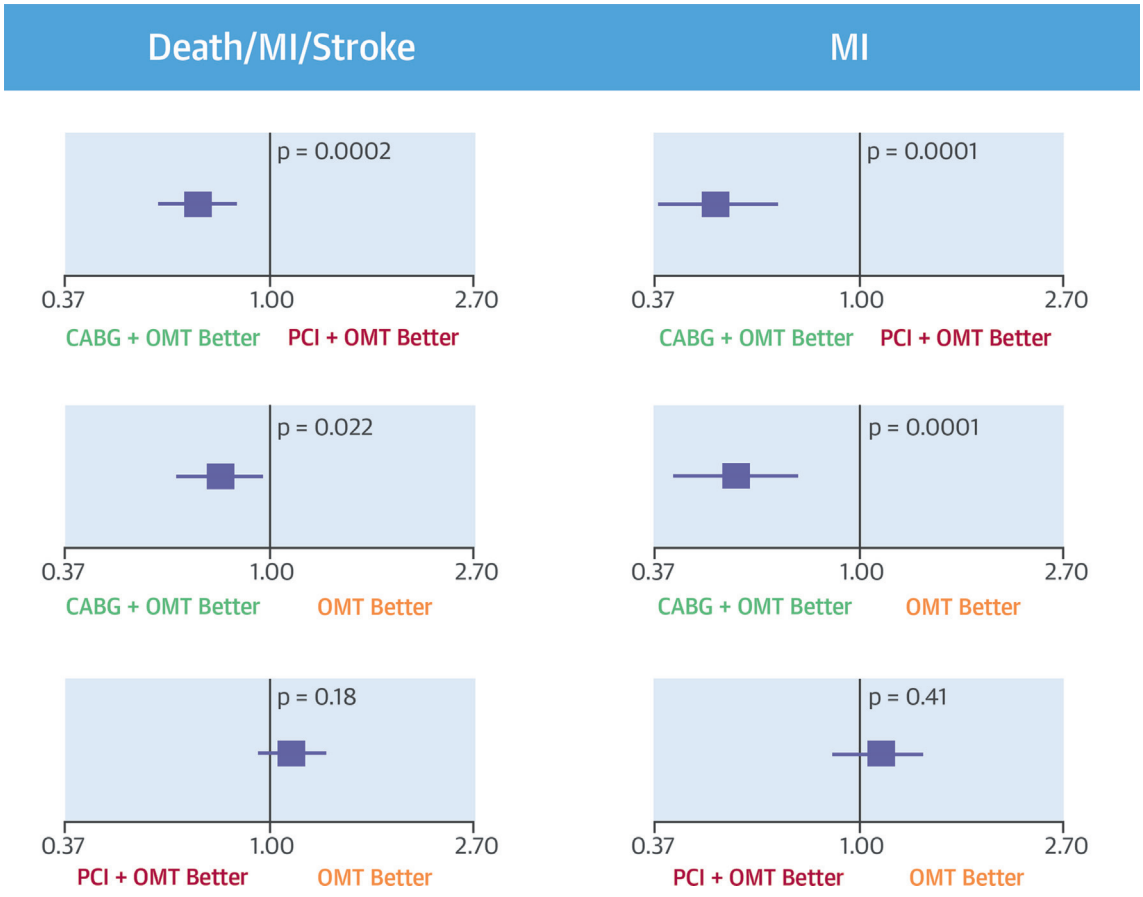
DISCUSSION

This unique patient-level pooled analysis in over 5,000 patients with stable CAD and T2DM who received OMT with or without revascularization showed that CABG + OMT is the preferred treatment strategy for most patients with T2DM because it reduced the risk of the primary composite of death, MI, or stroke by 29% compared with PCI + OMT and by 21% compared with OMT alone over a median follow-up of 4.5 years. Of the components of the primary endpoint, the CABG + OMT strategy significantly reduced overall mortality by 24% and risk of MI by 50% when compared with PCI + OMT (**Central Illustration**). When compared with OMT alone, CABG + OMT reduced the risk of MI by 45%, whereas death was not statistically reduced. All analyses of stroke events were nonsignificant over this time interval. Finally, comparisons of OMT and PCI + OMT were uniformly nonsignificant.

This pooled analysis is the largest study dedicated to assessing outcomes in patients with T2DM with stable CAD (n = 5,034). It utilizes the power of patient-level data, including coronary anatomy and LVEF, and it represents both the entire spectrum of CAD burden and the entire spectrum of available treatment strategies, ranging from modern OMT alone (25) to PCI + OMT (94% received stents), and finally, CABG + OMT (94% received arterial conduits). Accordingly, this pooled analysis provides the most relevant information applicable to the diverse management situations facing clinicians who must counsel all manner of patients with T2DM and stable CAD. But, when using a very conservative threshold for statistical significance, most subgroup analyses were neutral across the 3 treatment options. The exceptions were patients with 3-vessel disease, who derived a 28% reduction, and patients with normal LVEF, who derived a 29% reduction in the composite endpoint with CABG + OMT, compared with PCI + OMT. The remaining analyses provide information regarding outcomes, and they require further prospective study. However, there is a consistent pattern observed in these outcome observations in that all HR point estimates were <1.0 in comparisons between CABG + OMT and either PCI + OMT or OMT alone, favoring CABG + OMT. Conversely, most were >1.0 in comparing PCI + OMT with OMT alone, favoring OMT alone.

Although meta-analyses of larger numbers of studies in persons with T2DM and stable CAD have been published, only 1 used patient-level data, all are constrained to the subset with multivessel CAD, and none were able to assess the relative role of OMT alone (8-21). The patient-level meta-analysis performed by Hlatky et al. (19) analyzed 10 randomized trials with respect to overall mortality, but 6 of those trials were from the balloon angioplasty era, with the

CENTRAL ILLUSTRATION **Revascularization Strategies for Patients With Coronary Disease and Type 2 Diabetes Mellitus: Trial-Adjusted Hazard Ratios for 5 Years**



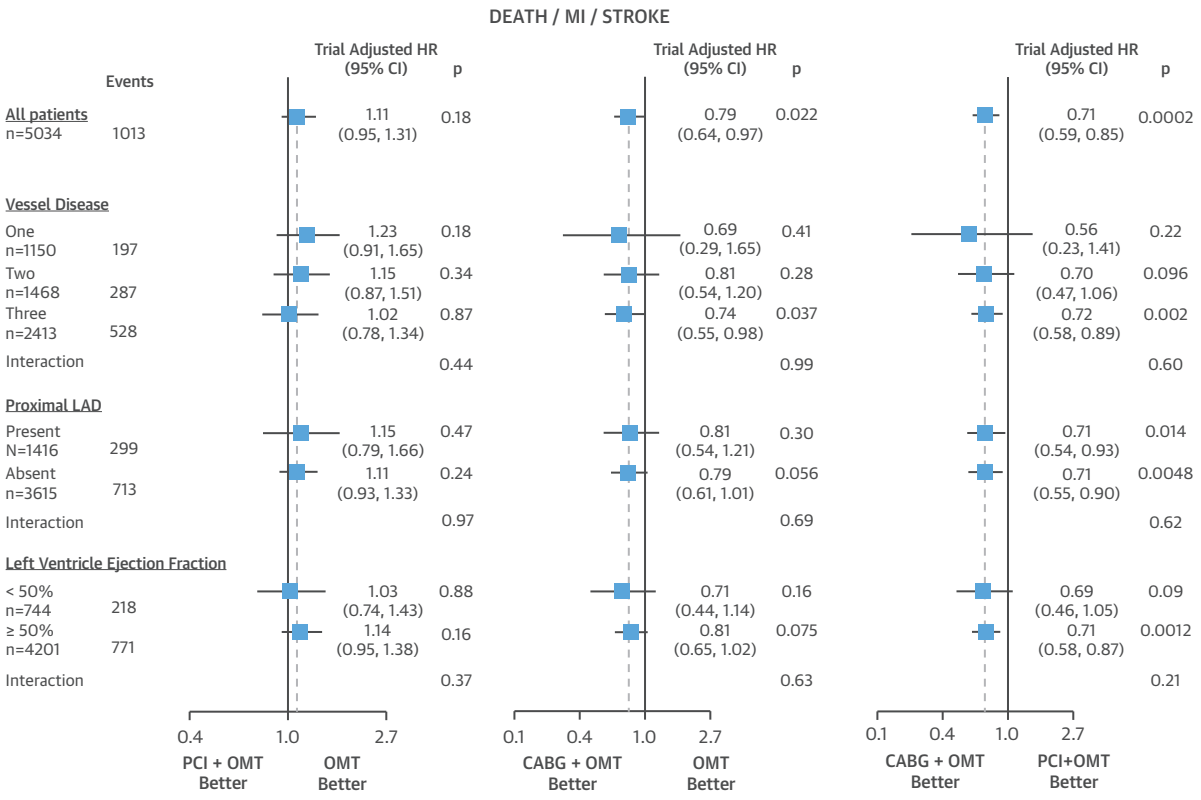
Mancini, G.B.J. et al. J Am Coll Cardiol. 2016;68(10):985–95.

Trial-adjusted hazard ratios for 5 years (death/MI/stroke) and MI. CABG = coronary artery bypass graft; MI = myocardial infarction; OMT = optimal medical therapy; PCI = percutaneous coronary intervention.

remainder from the bare-metal stent era. In the subset of patients with T2DM (n = 3,131), mortality was reduced by 30% in CABG-treated subjects. Angiographic features, numbers of diseased vessels, and presence of pLAD were not found to influence outcome, but these analyses were not reported specifically in the T2DM subgroup. Verma et al. (11) performed a meta-analysis of 8 trials that reported results separately for patients with diabetes (n = 3,612) and utilized arterial conduits or stents in ≥80% of patients randomized to CABG or PCI, respectively. They confirmed a long-term mortality reduction in CABG-treated patients with T2DM and multivessel CAD, which was irrespective of the use of either bare-metal or drug-eluting stents, but potential modulation of treatment effects on the basis of LVEF or CAD burden was not studied. Although not our primary endpoint, our study demonstrates and further supports a mortality reduction of 22% with CABG + OMT compared with PCI + OMT, but not compared with OMT alone. What is remarkably consistent, however, is the 45% to 50% reduction in MI among patients with T2DM and stable CAD who are treated with an initial CABG + OMT strategy, compared with either OMT alone or PCI + OMT strategies.

Our attempt to analyze outcomes in patients with pLAD was impeded by small sample size, reflecting the difficult, "real-world" challenge of enrolling such patients into trials. However, CABG + OMT showed a consistent point estimate reduction of 29% with CABG + OMT compared with PCI + OMT in the presence or absence of pLAD (**Figure 2**).

FIGURE 2 Forest Plots for Analyses on the Basis of the Composite Endpoint, With Subgroups Defined by Angiographic Parameters



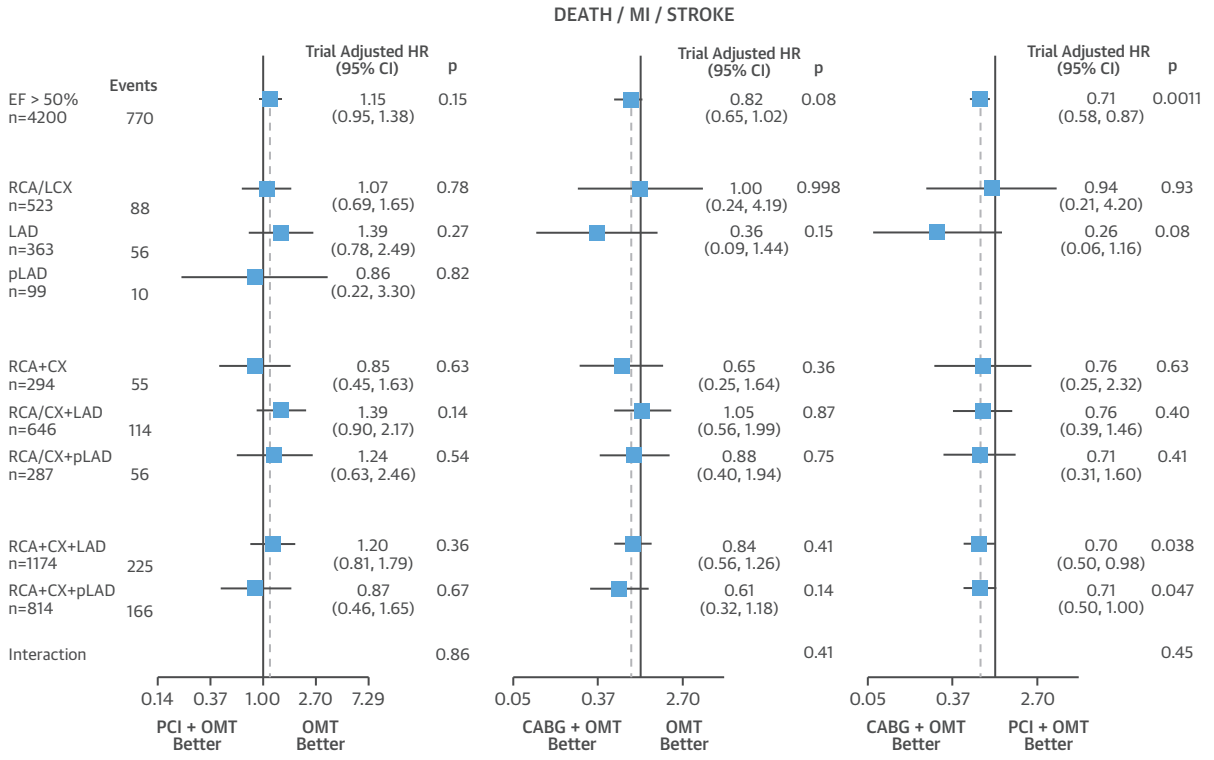
CI = confidence interval; HR = hazard ratio; LAD = left anterior descending; other abbreviations as in Figure 1.

The assessment of treatment by LVEF status was also limited by the fact that only 15% (n = 744) of the cohort had LVEF <50%, and the trials included too few patients with markedly depressed (<30%) LVEF. Although the analyses in this subgroup did not reach statistical significance, the observed risk reduction of 31% with CABG + OMT compared with PCI + OMT (p = 0.09) was very similar to the significant 29% risk reduction (p = 0.0012) observed in subjects with normal LVEF.

All patients were prescribed OMT with medications likely to exert benefit through reduction of coronary plaque progression, rupture, and erosion (26). Importantly, CABG provides a high flow conduit that can maintain adequate myocardial perfusion, not only beyond the initially bypassed stenosis, but also when new stenosis occurs more proximal to the anastomosis. In contrast, the PCI procedure is affected by stent or peristent complications (seen more commonly in patients with diabetes), as well as by progression, disruption, and erosion proximal and distal to the focally treated areas, and in nontarget vessels (26,27). Because the atherosclerotic process in T2DM is diffuse and extensive and progresses aggressively, these changes are more likely to lead to events if the subtended myocardium is not supplied by a graft. Additionally, the collateralization process, which results in a "natural" bypass, is well known to be impaired in subjects with T2DM, and may thereby impart a higher residual risk in patients treated with PCI and OMT alone than in CABG-treated patients (28). Finally, CABG may be associated with fewer regions of residual ischemic myocardium in the presence of total occlusions or with other circumstances precluding complete revascularization with PCI (29). Accordingly, these physiological and mechanistic factors may explain the superiority of CABG + OMT in patients with T2DM and stable CAD, particularly with respect to prevention of MI.

Wider clinical acceptance of CABG + OMT as the primary treatment strategy for persons with T2DM and stable CAD is often limited by concerns regarding early stroke and perioperative mortality. The increased risk of stroke in patients with CABG is

FIGURE 3 **Forest Plots for Analyses on the Basis of the Composite Endpoint for Patients With Normal Left Ventricular EF (≥50%) and Stratified by Specific Patterns of Coronary Artery Disease**



See Online Figure 3 for analyses in patients with low EF. CX = circumflex artery; EF = ejection fraction; LCX = left circumflex artery; pLAD = proximal left anterior descending; RCA = right coronary artery; other abbreviations as in Figures 1 and 2.

multifactorial (30). In a meta-analysis of 8 studies, Verma et al. (11) reported that stroke was significantly increased with CABG over PCI, even over 5 years of follow-up, but our results are discordant with those findings. Stroke was the least frequent event (n = 136), and was not significantly increased over the long term. And, of particular note, these events were clearly offset by the overall reductions in death and MI, yielding a significant reduction in risk of the primary composite endpoint over a 5-year period (Table 2).

STUDY LIMITATIONS. SYNTAX scoring was performed prospectively only in the FREEDOM trial (24). The segmental coronary detail collected for this analysis constitutes some of the information required to calculate the SYNTAX score, but the additional details that might help decide whether to deviate from a CABG + OMT strategy are not available. This does not detract from the simple and commonly used characterization of patterns of angiographic CAD described in this study. SYNTAX scoring has not uniformly discriminated optimal treatment strategy in clinical trial settings, including in patients with T2DM; is not easily calculated during routine angiography; and is not used widely in general practice (24,31-37). Moreover, low scores may be misinterpreted as being permissive for a PCI + OMT strategy through emphasis on feasibility of PCI, instead of a focus on feasibility of CABG. The use of bare-metal and drug-eluting stents was considered in the aggregate, and appears to be justified on the basis of prior analyses showing no definitive outcome benefit between these 2 stent types for the composite of death or death and MI, and no outcome differences compared with CABG when even newer-generation drug-eluting stents are used (12,33,34). A recently published trial (35) shows advantages of everolimus-eluting over paclitaxel-eluting stents in patients with T2DM. However, these benefits were primarily observed with respect to target vessel failure and need for revascularization, the study was short in

duration (only 1 year), 70% of patients had single-vessel CAD, 50% had unstable angina or acute coronary syndrome, and there were no OMT or CABG arms, which are important considerations if one is to compare, as was our goal, the effects of the full spectrum of management options on hard clinical endpoints. Moreover, rates of major adverse cardiovascular events were still higher in a long-term trial among everolimus-treated compared with CABG-treated patients, including augmented rates of MI (34). Clearly, any prospective, contemporary trial will need to incorporate state-of-the-art therapies, but these may not pertain solely to PCI technology but also to CABG, as well as new therapeutic options for medically managing T2DM (36–43). We have already highlighted the limitation of recruiting a sufficient number of patients with low LVEF or pLAD involvement, and all 3 trials excluded subjects with left main CAD. We did not undertake a comparison of patients with or without complete revascularization, nor were measures of fractional flow reserve or quantitation of induced ischemia available in all patients. The latter is relevant to the ongoing ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) trial of subjects with stable CAD and moderate to severe ischemia, including patients with T2DM, who are being randomized prospectively to a conservative versus invasive management strategy where the primary endpoint is a composite of long-term cardiovascular mortality or nonfatal MI (44).

CONCLUSIONS

For most patients with T2DM and stable CAD, this patient-level pooled analysis provides compelling clinical evidence that CABG + OMT is the preferred treatment strategy because it reduces the primary composite of death, MI, or stroke during a 5-year follow-up, including significant reduction of death and MI compared with a PCI + OMT strategy, and a reduction of MI compared with an OMT-only strategy. In the presence of factors that preclude a CABG + OMT strategy, we provide strong evidence to support OMT alone as the next best therapeutic approach. When such patients do not achieve sufficient control of angina or an adequate quality of life with OMT alone, PCI + OMT should be considered an appropriate therapeutic option.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: A meta-analysis of patient-level data from clinical trials of patients with T2DM and CAD suggests that coronary bypass surgery plus guideline-directed medical therapy (CABG + OMT) reduces the composite incidence of death, MI, or stroke over 5 years of follow-up compared with PCI. In patients with comorbidities that preclude CABG + OMT, medical therapy without revascularization is associated with better outcomes than PCI.

TRANSLATIONAL OUTLOOK: Further studies are warranted to identify optimal treatment strategies for specific subgroups of patients with T2DM, such as those with stenosis of the pLAD artery or reduced left ventricular systolic function.

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KEY WORDS coronary artery bypass grafting, optimal medical therapy, percutaneous coronary intervention, stable ischemic heart disease

APPENDIX For an expanded Methods section and supplemental figures and tables, please see the online version of this article.