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ORIGINAL INVESTIGATIONS

Long-Term Outcome of PCI Versus CABG in Insulin and Non–Insulin-Treated Diabetic Patients

Results From the FREEDOM Trial

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ABSTRACT

BACKGROUND The prospective, randomized FREEDOM (Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes) trial found coronary artery bypass graft surgery (CABG) was associated with better clinical outcomes than percutaneous coronary intervention (PCI) in patients with diabetes and multivessel disease, managed with or without insulin.

OBJECTIVES In this subgroup analysis of the FREEDOM trial, we examined the association of long-term clinical outcomes after revascularization in patients with insulin-treated diabetes mellitus (ITDM) compared with patients not treated with insulin.

METHODS A total of 1,850 FREEDOM subjects had an index revascularization procedure performed: 956 underwent PCI with drug-eluting stents (DES), and 894 underwent CABG. A total of 602 patients (32.5%) had ITDM (PCI/DES n = 325, 34%; CABG n = 277, 31%). Subjects were classified according to ITDM versus non-ITDM, with comparison of PCI/DES versus CABG for each group. Interaction analyses were performed for treatment by diabetes mellitus (DM) status alone and for treatment by DM status by coronary lesion complexity. Analyses were performed for the primary outcome composite of death/stroke/myocardial infarction (MI) using all available follow-up data.

RESULTS The overall 5-year event rate of death/stroke/MI was significantly higher in ITDM versus non-ITDM patients (28.7% vs. 19.5%, $p < 0.001$), which persisted even after adjustment for multiple baseline factors, angiographic complexity, and revascularization treatment group (death/stroke/MI hazard ratio [HR]: 1.35, 95% confidence interval [CI]: 1.06 to 1.73, $p = 0.014$). With respect to the primary composite endpoint, CABG was superior to PCI/DES in both DM types and the magnitude of treatment effect was similar (interaction $p = 0.40$) for ITDM (PCI vs. CABG HR: 1.21; 95% CI: 0.87 to 1.69) and non-ITDM patients (PCI vs. CABG HR: 1.46; 95% CI 1.10 to 1.94), even after adjusting for the angiographic SYNTAX score level. Based on 5-year event rates, the number needed to treat with CABG versus PCI to prevent 1 event is 12.7 in ITDM and 13.2 in non-ITDM.

CONCLUSIONS In patients with diabetes and multivessel coronary artery disease, the rate of major adverse cardiovascular events (death, MI, or stroke) is higher in patients treated with insulin than in those not treated with insulin. Furthermore, we did not detect a significant difference in the magnitude of PCI versus CABG treatment effect for patients treated with insulin and those not treated with insulin. (Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes [FREEDOM]; NCT00086450) (J Am Coll Cardiol 2014;64:1189–97) © 2014 by the American College of Cardiology Foundation.

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

BUN = blood urea nitrogen

CABG = coronary artery bypass graft surgery

CI = confidence interval

DES = drug-eluting stent(s)

DM = diabetes mellitus

HR = hazard ratio

ITDM = insulin-treated diabetes mellitus

ITT = intention-to-treat

MI = myocardial infarction

MVD = multivessel coronary disease

PCI = percutaneous coronary intervention

The global prevalence of diabetes mellitus (DM) among adults is currently estimated to exceed 6.4% (285 million individuals) and is projected to grow to 7.7% (439 million individuals) by 2030, making diabetes and its complications important public health problems (1). Currently, approximately 26% of the U.S. patients with diabetes are treated with insulin (ITDM) (2), and these patients are known to be at higher risk for complications after coronary reperfusion than both patients with non-ITDM and patients without diabetes (3,4). DM plays an important role in accelerated atherogenesis and atherothrombosis (5), and patients with diabetes are prone to develop multivessel coronary disease (MVD) (6–8). Despite a high technical success rate with MVD stenting, those treated with insulin have a higher rate of coronary artery bypass graft surgery (CABG) or repeat percutaneous coronary intervention (PCI), a higher risk of stent thrombosis, and lower 1-year survival than nondiabetic patients (9,10). Recently, the FREEDOM (Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes) trial demonstrated that for patients with diabetes and MVD, CABG is superior to PCI with drug-eluting stents (DES) in that it significantly reduced rates of death and myocardial infarction (MI), albeit with a higher rate of stroke (11). Previous CABG reports had shown that ITDM patients have a particularly elevated risk of in-hospital morbidity and wound infections after CABG, leading to a prolonged length of hospital stay, elevated 30-day mortality, and increased risk of readmission for cardiac causes (12–14).

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The aims of the present study were: 1) to provide a baseline clinical and angiographic description of the ITDM and non-ITDM groups; 2) to examine whether CABG and/or PCI/DES outcomes depend on ITDM status; and 3) to examine the association of ITDM status with the difference between CABG- and PCI/DES-treated patients in the primary composite outcome of death from any cause, nonfatal MI, or nonfatal stroke.

TABLE 1 Baseline and Procedural Characteristics by ITDM Status

	Non-ITDM (n = 1,248)	ITDM (n = 602)	p Value
Age, yrs	63.2 ± 8.9	62.6 ± 9.2	0.16
Male	76.5	61.3	<0.0001
Body mass index, g/m^2	29.3 ± 5.0	30.5 ± 5.9	<0.0001
Duration of diabetes, yrs	7.7 ± 7.2	15.1 ± 9.9	<0.0001
Hemoglobin A_{1c}, %	7.5 ± 1.6	8.5 ± 1.8	<0.0001
BUN, mg/dl	21.0 (15.4–32.0)	23.1 (16.1–36.0)	0.02
History of hypertension	(83.2)	87.5	0.02
Peripheral neuropathy	5.2	14.3	<0.0001
Current smoker	14.7	17.9	0.07
Previous MI	25.8	25.6	0.92
Previous stroke	3.1	3.8	0.44
Congestive heart failure	24.3	32.1	0.0004
NYHA functional class I	75.7	67.9	0.0004
Number of diseased vessels			
2	17.7	14.8	0.13
3	82.3	85.2	
Total lesion length, mm	77.2 ± 33.8	79.0 ± 33.0	0.26
Any total occlusion in LAD, RCA, or LCx	23.2	23.0	0.92
LV ejection fraction	66.3 ± 11.1	65.7 ± 11.9	0.34
EuroSCORE	2.5 ± 2.4 1.7 (1.2–3.0)	2.9 ± 2.4 2.1 (1.3–3.0)	<0.0001
SYNTAX score	26.0 ± 8.6 26.0 (19.5–31.0)	26.4 ± 8.5 26.0 (20.0–31.0)	0.33
Acute coronary syndrome	28.6	35.1	0.005
Number of PCI lesions	3.5 ± 1.4	3.5 ± 1.4	0.97
Number of CABG grafts	2.9 ± 0.8	3.0 ± 0.8	0.05

Values are mean ± SD, %, or median (interquartile range).

BUN = blood urea nitrogen; CABG = coronary artery bypass graft surgery; ITDM = insulin-treated diabetes mellitus; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LV = left ventricular; MI = myocardial infarction; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; RCA = right coronary artery.

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TABLE 2 Baseline and Procedural Characteristics by ITDM Status and Treatment Arm

	Non-ITDM			ITDM		
	PCI (n = 631)	CABG (n = 617)	p Value	PCI (n = 325)	CABG (n = 277)	p Value
Age, yrs	63.2 ± 8.8	63.3 ± 9.1	0.85	63.2 ± 9.2	61.9 ± 9.2	0.08
Male	79.1	73.9	0.03	61.9	60.7	0.76
Body mass index, g/m^2	29.1 ± 4.9	29.6 ± 5.1	0.04	30.6 ± 6.0	30.3 ± 5.8	0.54
Duration of diabetes, yrs	7.5 ± 7.3	8.0 ± 7.2	0.27	15.1 ± 9.9	15.1 ± 10.0	0.99
Hemoglobin A_{1c}, %	7.5 ± 1.6	7.5 ± 1.6	0.56	8.5 ± 1.8	8.5 ± 1.7	0.89
BUN, mg/dl	21.0 (15.4–32.0)	21.4 (15.3–32.0)	0.79	23.9 (16.7–36.0)	22.2 (16.0–36.0)	0.33
History of hypertension	83.2	83.1	0.98	86.8	88.5	0.53
Peripheral neuropathy	4.3	6.2	0.14	15.4	13.0	0.40
Current smoker	13.2	16.2	0.13	18.2	17.7	0.88
Previous MI	25.8	25.8	0.98	25.5	25.6	0.98
Previous stroke	2.9	3.4	0.58	5.5	1.8	0.02
Congestive heart failure	23.8	24.8	0.67	28.3	36.5	0.03
NYHA functional class I	76.2	75.2	0.67	71.7	63.5	0.03
Diseased vessels						
2	18.3	17.0	0.53	16.1	13.4	0.36
3	81.7	83.0		84.0	86.6	
Any total occlusion in LAD, RCA, or LCx	21.9	24.5	0.27	24.3	21.4	0.39
LV ejection fraction	65.9 ± 11.9	66.8 ± 10.2	0.23	65.3 ± 12.5	66.1 ± 11.1	0.47
EuroSCORE	2.5 ± 2.2 1.7 (1.2–2.9)	2.6 ± 2.5 1.7 (1.3–3.1)	0.49	3.0 ± 2.6 2.1 (1.3–3.6)	2.8 ± 2.3 2.1 (1.3–3.6)	0.61
SYNTAX score	26.1 ± 8.3 26 (20–31)	25.8 ± 8.9 25 (19–31)	0.50	26.3 ± 8.5 25 (21–31)	26.5 ± 8.5 26.8 (20–32)	0.73
Acute coronary syndrome	30.0	27.2	0.29	34.5	35.7	0.74
No. PCI lesions	3.5 ± 1.4			3.5 ± 1.4		
No. CABG grafts		2.9 ± 0.8			3.0 ± 0.8	

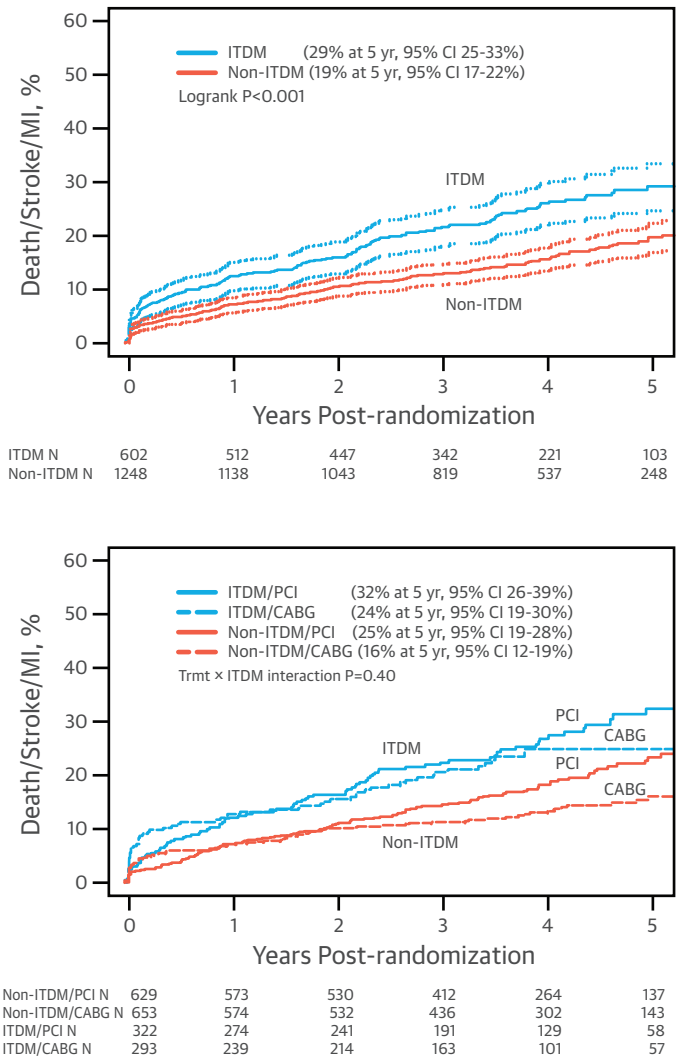
Values are mean ± SD, %, or median (interquartile range).
Abbreviations as in Table 1.

METHODS

The patient population in the FREEDOM trial has been described in detail previously (11,15). In brief, the multicenter, open-label prospective randomized superiority trial evaluated PCI/DES versus CABG in 1,900 diabetic patients in whom revascularization was indicated with stenosis of more than 70% in 2 or more major epicardial vessels, involving at least 2 separate coronary artery territories, and without left main coronary stenosis. Consenting diabetic patients with MVD were randomized on a 1:1 basis to either CABG or multivessel stenting with DES and observed up to 7 years (minimum 2 years; median 4 years). Patients randomized to the PCI/DES arm received any approved DES (sirolimus-eluting and paclitaxel-eluting were the predominant stents) per operator's choice. In this post-hoc analysis, we classified subjects into PCI/DES versus CABG based on the actual treatment received (non-intention-to-treat [ITT]) and analyzed outcomes occurring post-procedure: 1,850 FREEDOM subjects with this definition had an index procedure: 956 PCI and 894 CABG procedures were performed.

MEASURES. Patients were categorized as ITDM if they indicated baseline use of insulin (either alone or in combination with other oral antidiabetic medication). To systematically assess angiographic complexity, SYNTAX (Synergy Between PCI With TAXUS and Cardiac Surgery) score (16), including chronic total occlusions, were calculated and evaluated based on angiographic core laboratory interpretations conducted at the Cardiovascular Research Foundation in New York, New York. Overall, chronic total occlusion and bifurcation statistics were based on total number of lesions (N = 11,219), and not on number of subjects. The primary outcome was the composite (earliest occurring) of all-cause death/MI/stroke using all available follow-up data.

STATISTICS. Categorical variables are described using a count and percentage, and continuous variables by mean and SD, or median and interquartile range. The distributions of categorical variables by



CENTRAL ILLUSTRATION Estimates of the Primary Endpoint by Treatment Received and Insulin Use

(Top) Kaplan-Meier estimated percentage of subjects achieving the primary composite outcome by insulin use, with point-wise 95% confidence bands (**salmon** = non-ITDM; **blue** = ITDM). **(Bottom)** Kaplan-Meier estimated percentage of subjects achieving the primary composite outcome by treatment received and insulin use (interaction p = 0.40). The median follow-up was somewhat lower in the CABG survivors within the ITDM cohort (42.7 months) compared with the other 3 groups (median 48.0 months for PCI ITDM; 47.6 months for PCI non-ITDM; 48.0 for CABG non-ITDM). CABG = coronary artery bypass graft surgery; CI = confidence interval; ITDM = insulin-treated diabetes mellitus; MI = myocardial infarction; PCI = percutaneous coronary intervention; Trmt = treatment.

treatment group and by ITDM status were compared using a Fisher exact test. The Wilcoxon rank sum test was used to compare the distributions of blood urea nitrogen (BUN), creatinine, euroSCORE, by treatment arm and by ITDM status, whereas the Student *t* test was used for the remaining continuous variables. Event-free survival rates were estimated using the Kaplan-Meier method, and the time to event for ITDM versus non-ITDM patients was compared using the log-rank test, using all available follow-up data. Two- and 5-year point estimates are presented. For the primary endpoint and secondary endpoints, a Cox proportional hazards regression test of interaction (treatment received by ITDM status) was used to assess whether there was a differential treatment effect by ITDM status using all available follow-up. Multivariable Cox regression of the primary endpoint was utilized to identify whether ITDM status is an independent predictor of outcome. Key results also are presented in the ITT population and contained in the Online Appendix. To construct the multivariable model, we first examined univariate Cox models, and variables that were at least marginally associated with the endpoint ($p < 0.20$) were included in a model in which stepwise selection was used for predictor selection at each step. Additional candidate variables were included into the multivariable model if there were significant treatment by predictor interactions ($p \leq 0.05$). Finally, we also included measures that were significant predictors of ITDM status. Subgroup analyses were performed for ITDM status and treatment group, according to the angiographic SYNTAX score. Our findings are reported as hazard ratios (HRs) with 95% confidence intervals (CIs). A p value <0.05 was considered significant.

RESULTS

Nearly one-third (32.5%) of subjects had ITDM (602 of 1,850). As summarized in **Table 1**, ITDM was more prevalent in females (38.7% vs. 23.5%) and in patients with a history at baseline of hypertension (87.5% vs. 83.2%), peripheral neuropathy (14.3% vs. 6.2%), congestive heart failure (32.1% vs. 24.3%), and acute coronary syndrome (35.1% vs. 28.6%). ITDM was also significantly associated with higher baseline body mass index (BMI) (30.5 ± 5.9 g/m^2 vs. 29.3 ± 5.5 g/m^2), longer duration of diabetes (mean 15.1 ± 9.9 vs. 7.7 ± 7.2 years), and higher hemoglobin A_{1c} (8.5 ± 1.8% vs. 7.5 ± 1.6%), BUN (median 23.1 vs. 21.0 mg/dl), and EuroSCORE (median 2.1 vs. 1.7). Baseline medications associated with ITDM were anticoagulants (21% ITDM vs. 12% non-ITDM; primarily heparin, 19% ITDM vs. 11% non-ITDM), antiangina agents (91% vs. 87%), lipid-lowering agents (89% vs. 84%), and other cardiac medical therapy (88% vs. 80%; primarily loop diuretics and angiotensin-converting enzyme inhibitors) (Online Table 1).

In **Table 2**, we summarized the patient baseline characteristics within the ITDM versus non-ITDM

subgroups for patients treated with PCI/DES versus CABG. In the ITDM group, PCI subjects were more likely to have a history of stroke (5.5% vs. 1.8%) and be in New York Heart Association functional class I (72% vs. 64%), whereas the CABG group had a higher rate of congestive heart failure (37% vs. 28%). There were no baseline medication differences except for more PCI patients being on loop diuretics compared with those who underwent CABG (20% vs. 12%) (Online Table 2).

In the non-ITDM group, we found that CABG subjects were more likely to be female (26% vs. 21%), have a slightly higher BMI, were more often in angina class 0 to I (70% vs. 65%), and have a higher mean glucose level on the day of the procedure (median 149.4 vs. 140.4 mg/dl) (**Table 2**). There were no medication differences at baseline except for PCI subjects being more likely than CABG subjects to receive clopidogrel (27% vs. 19%) (Online Table 2).

The **Central Illustration** displays the higher event rate for patients with ITDM versus non-ITDM (28.7% vs. 19.5% for the trial primary outcome at 5 years, $p < 0.001$) (ITT analysis in the Online Figure 1). Similarly, time to event was strongly associated with duration of diabetes ($p = 0.007$). The event rates were 24.4% versus 20.7% for patients with diabetes duration ≥9 years and <9 years, respectively. For all trial endpoints except 30-day repeat revascularization, ITDM patients had a significantly higher event rate, with a consistent approximately 1.5-fold greater risk than non-ITDM patients (**Table 3**).

In multivariable analysis of baseline factors and treatment group, we found that ITDM status was an independent predictor of the primary outcome, with ITDM patients having an approximately 1.5-fold increase in event rate compared with patients without ITDM (death/stroke/MI HR: 1.35; 95% CI: 1.06 to 1.73; $p = 0.014$). The model controlled for: EuroSCORE, hemoglobin A_{1c}, chronic renal insufficiency, BUN, age, history of stroke, history of MI, low-density lipoprotein cholesterol, heart rate, left ventricular ejection fraction, and revascularization treatment received (CABG vs. PCI/DES).

The treatment effect of CABG versus PCI in the 2 subsets of DM types is shown in **Table 4** and the **Central Illustration** (ITT analysis in Online Figure 2). With respect to the primary composite endpoint, there was no significant interaction of treatment and DM type ($p = 0.40$) (**Table 4**, **Central Illustration**); there is insufficient evidence to declare a differential treatment effect in ITDM (PCI vs. CABG HR: 1.21; 95% CI: 0.87 to 1.69; $p = 0.009$) and non-ITDM patients (PCI vs. CABG HR: 1.46; 95% CI: 1.10 to

TABLE 3 ITDM Versus Non-ITDM Hazard Ratios for FREEDOM Trial Outcomes

Endpoint	ITDM vs. Non-ITDM Hazard Ratio	95% CI	p Value*
Death/stroke/MI	1.63	1.32–2.02	<0.001
All-cause mortality	1.54	1.16–2.05	0.003
Stroke	1.86	1.07–3.02	0.026
MI	1.64	1.18–2.30	0.004
CV death	1.58	1.11–2.26	0.012
30-day MACCE	1.54	1.02–2.33	0.040
1-yr MACCE	1.51	1.18–1.92	0.001
30-day repeat revascularization	1.20	0.64–2.27	0.57
1-yr repeat revascularization	1.44	1.05–1.97	0.025

Hazard ratios are based on all available follow-up for the primary endpoint and its components. *Cox proportional hazards regression Wald test.

CI = confidence interval; CV = cardiovascular; FREEDOM = Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes; MACCE = major adverse cardiac and cerebrovascular event(s); other abbreviations as in **Table 1**.

TABLE 4 Kaplan-Meier Event-Free Estimated Event Rates for CABG Versus PCI

	Non-ITDM			ITDM			Treatment × Insulin Interaction
Endpoint (%)	PCI	CABG	PCI vs. CABG	PCI	CABG	PCI vs. CABG	p Value*
5-yr all-cause death/stroke/MI	23.2 (19.4–27.7)	15.6 (12.5–19.5)	1.46 (1.10–1.94)	32.2 (26.3–39.0)	24.3 (19.1–30.5)	1.21 (0.87–1.69)	0.40
5-yr all-cause mortality	14.5 (11.2–18.6)	9.3 (6.9–12.5)	1.36 (0.94–1.96)	19.0 (14.2–25.0)	14.1 (10.1–19.5)	1.19 (0.76–1.85)	0.64
5-yr stroke	1.7 (0.9–3.2)	4.3 (2.7–6.8)	0.51 (0.25–1.06)	3.7 (2.0–6.9)	7.5 (4.5–12.5)	0.60 (0.28–1.30)	0.77
5-yr MI	11.9 (9.1–15.6)	4.8 (7.4–3.1)	2.32 (1.45–3.70)	17.7 (12.8–24.3)	8.6 (5.6–23.0)	1.68 (0.99–2.83)	0.37
5-yr CV death	9.3 (6.7–12.9)	5.5 (8.1–3.7)	1.34 (0.84–2.13)	12.9 (8.9–18.6)	8.9 (5.8–13.5)	1.22 (0.70–2.12)	0.78
30-day MACCE	4.1 (2.8–6.0)	4.4 (3.0–6.3)	0.94 (0.55–1.61)	6.2 (4.0–9.4)	6.9 (4.4–10.6)	0.89 (0.48–1.67)	0.90
1-yr MACCE	14.7 (12.1–17.7)	10.3 (8.2–13.0)	1.43 (1.04–1.98)	20.7 (16.6–25.5)	15.4 (11.6–20.3)	1.35 (0.92–1.98)	0.81
30-day repeat revascularization	2.7 (1.7–4.3)	1.5 (0.8–2.8)	1.86 (0.83–4.17)	4.3 (2.6–7.2)	0.4 (0.1–2.7)	12.10 (1.59–92.0)	0.09
1-yr repeat revascularization	10.8 (8.6–13.5)	4.7 (3.2–6.7)	2.38 (1.53–3.70)	16.1 (12.5–20.6)	4.9 (2.9–8.4)	3.47 (1.89–6.39)	0.33

Values are HR (95% CI). The 95% CI and HRs are based on adjudicated events and interaction p value for treatment by insulin dependency status. HR estimates are based on all available follow-up for the primary endpoint and its components. *p Value from Cox regression test of treatment × subgroup interaction using all available follow-up data (i.e., >5 years).

HR = hazard ratio; other abbreviations as in **Tables 1 and 3**.

TABLE 5 5-Year Kaplan-Meier Estimated Event Rates for the Primary Endpoint (Death/Stroke/MI)

	Non-ITDM			ITDM			Treatment × Insulin Interaction
Group*	PCI	CABG	PCI vs. CABG	PCI	CABG	PCI vs. CABG	p Value
SYNTAX ≤22 (208, 231, 123, 93)	19.7 (13.0–24.4)	14.1 (9.5–20.75)	1.18 (0.71–1.96)	29.7 (20.2–42.3)	26.3 (17.7–38.0)	0.84 (0.47–1.48)	0.39
SYNTAX 23–32 (305, 255, 138, 129)	23.1 (17.8–29.7)	14.3 (10.1–20.0)	1.61 (1.04–2.49)	35.5 (26.8–46.0)	21.8 (15.2–30.7)	1.56 (0.95–2.57)	0.93
SYNTAX ≥33 (114, 125, 64, 54)	30.4 (20.9–42.8)	20.0 (12.8–30.4)	1.58 (0.88–2.81)	28.9 (19.3–42.0)	25.9 (15.3–41.9)	1.27 (0.61–2.64)	0.65

Values are HR (95% CI). The 95% CI and HR are based on adjudicated events for the primary endpoint (death/stroke/MI) using all available follow-up and interaction p value for treatment by insulin dependency status, at each level of angiographic complexity. p Values were derived from Cox regression test of treatment × subgroup interaction using all available follow-up data (i.e., >5 years). *Numbers in parentheses indicate PCI n, CABG n for each stratum.

Abbreviations as in Tables 1 and 3.

1.94; p = 0.33). The results for the ITT population are provided in the Online Figures 1 and 2, and are qualitatively identical to the non-ITT results, showing no significant interaction of treatment and DM type (p = 0.33) (PCI vs. CABG in ITDM [ITT] HR: 1.17; 95% CI: 0.85 to 1.63; p = 0.33 and PCI vs. CABG in non-ITDM [ITT] HR: 1.45; 95% CI: 1.10 to 1.92; p = 0.009).

To detect the observed PCI versus CABG HR of 1.2 with 85% power in the ITDM group at the 0.05 level would have required approximately 1,200 patients (i.e., double the size of the ITDM cohort in the FREEDOM trial).

We found a significant CABG benefit over PCI in non-ITDM patients, whereas because of insufficient power, our results do not provide sufficient evidence to state a CABG benefit in the ITDM subgroup. However, the hazard point estimates are in the same direction for both subgroups, as supported by the nonsignificant interaction test, demonstrating that ITDM/non-ITDM subgroup is not an effect modifier with regard to the benefit of CABG over PCI in patients with diabetes and MVD.

If the subgroup is disregarded, the HR was 1.38 (95% CI: 1.11 to 1.71; p = 0.004). Similarly, there was no interaction of treatment by duration of diabetes (p = 0.12 for continuous duration and p = 0.41 for duration <9 years vs. ≥9 years). Consistent with these findings, based on 5-year event rates, the number needed to treat with CABG versus PCI to prevent 1 event was similar for the 2 subgroups: 12.7 in ITDM and 13.2 in non-ITDM.

Treatment by DM group interactions were also analyzed within SYNTAX score-level (angiographic complexity), without finding any difference in the comparison of PCI/DES versus CABG effect size dependency on DM group (Table 5) with respect to the 5-year Kaplan-Meier estimated event rates and HRs based on adjudicated events for the primary endpoint of death/MI/stroke. Table 6 shows that there was no significant interaction with respect to the same 5-year outcome between the ITDM status and SYNTAX score.

We also explored whether the relative hazard of death/stroke/MI for PCI versus CABG patients was different in the first 2 years post-procedure compared with after 2 years, both in the overall cohort and within the ITDM and non-ITDM groups. There was evidence of nonproportional hazards (p < 0.001), with no significant PCI versus CABG effect before 2 years (HR: 1.11 overall, 1.06 for ITDM, 1.12 for non-ITDM), but an increased hazard for PCI patients after 2 years (HR: 2.06 overall, 1.52 for ITDM, 2.46 for non-ITDM) (Table 7).

TABLE 6 5-Year Kaplan Meier Estimated Event Rates With 95% CI and HR for the Primary Endpoint (Death/Stroke/MI) for ITDM Status by SYNTAX Score

Group*	ITDM 5-Yr Rate	Non-ITDM 5-Yr Rate	ITDM vs. Non-ITDM	ITDM × SYNTAX Interaction p Value
SYNTAX ≤22 (n = 216, 439)	28.5% (21.5–37.1)	16.4% (12.6–21.3)	1.90 (1.30–2.78)	
SYNTAX 23–32 (n = 267,560)	29.4% (23.5–36.4)	19.1% (15.5–23.4)	1.61 (1.17–2.22)	0.59
SYNTAX ≥33 (n = 118,239)	27.7% (20.1–35.5)	24.8% (32.6–18.7)	1.40 (0.88–2.21)	

The 95% CI and HR are based on adjudicated events for the primary endpoint (death/stroke/MI) using all available follow-up and interaction p value (Cox regression) for ITDM status by SYNTAX score. *The numbers in parentheses indicate ITDM n, non-ITDM n for each stratum.

Abbreviations as in Tables 1, 3, and 4.

DISCUSSION

In this secondary analysis of the FREEDOM trial, we examined the association of ITDM status and

clinical outcomes after revascularization with CABG or PCI/DES. Our main findings were: 1) clinical event rates were higher in patients with ITDM than in those not treated with insulin; and 2) there was no significant interaction of treatment and DM type, indicating that there is insufficient evidence to declare a differential treatment effect in ITDM and non-ITDM patients (**Central Illustration**). Although a nonsignificant interaction test does not definitively demonstrate that treatment effects within subgroups are similar, we do not feel that the HRs were highly clinically different. This also was maintained after angiographic stratification for lesion complexity. Indeed, the SYNTAX score derived from the baseline angiogram was similar in the 2 DM subgroups, which also is supported by the target lesion length being similar in the 2 ITDM and non-ITDM patient groups.

In addition, we observed that ITDM patients were more often female, had higher BMI, hemoglobin A_{1c}, and BUN levels than non-ITDM patients, and were more likely to have a history of stroke, hypertension, congestive heart failure, and acute coronary syndrome when compared with non-ITDM patients. A higher primary outcome event rate was associated with a longer duration of diabetes. However, similar to our primary finding using ITDM status, there was no significant interaction of revascularization mode and duration of insulin treatment.

There were very few differences in baseline characteristics between CABG and PCI/DES treatment within either the ITDM or the non-ITDM strata, and these differences were not variables that are known to be strong risk factors for adverse outcome. Earlier reports based on data from the CARDia (Coronary Artery Revascularization in Diabetes) trial (17) and the 5-year results of the SYNTAX trial (16) indicated significantly higher rates of major adverse cardiac and cerebrovascular events in patients with diabetes treated with PCI compared with those treated with CABG (18). The present analysis extends these findings by showing that regardless of ITDM status and SYNTAX score, CABG treatment is superior to PCI/DES, not only in repeat revascularization, but also in a significant reduction in all-cause death and MI in patients with diabetes and MVD.

Our results lend support to a recent meta-analysis of several randomized trials of CABG versus PCI, which found lower mortality rates in diabetic patients revascularized with CABG compared with PCI (19), as well as to prospective registry data of consecutive CABG patients that reported mortality to be significantly higher in patients with ITDM, compared with non-ITDM or non-diabetic patients (3). The increased stroke rate following CABG compared with PCI is also independent of ITDM status (5-year rates of 7.5% vs. 3.7% for CABG and PCI ITDM patients; and 4.3% vs. 1.7% for CABG and PCI non-ITDM patients). This is consistent with a prior meta-analysis reporting on post-CABG versus post-PCI stroke rates (post-CABG stroke rate at 1 year of 1.83%; odds ratio of 1.67 compared with PCI) (20).

We documented that insulin-treated patients have worse clinical outcome regardless of the treatment arm, which may either be due to more aggressive disease in these patients or an adverse effect of insulin.

Iatrogenic hyperinsulinemia controls hyperglycemia in ITDM but also may promote proinflammatory macrophage responses and stimulate hormonal overactivation of signal transduction pathways, which affects progression of atherogenesis and disturbs hemodynamic control and cardiovascular function by disrupting the balanced synthesis and release of endothelial mediators (21–23). The associated clinical manifestations described include essential hypertension (24), pathological cardiac hypertrophy with chronic pressure overload (25), as well as myocardial hypoxia (26), heart failure (27–29), and weight gain, in turn promoting proinflammatory effects (30). At the same time, insulin might be a marker of high-risk patients, not only because of more severe insulin resistance but also because of more prolonged DM (5,30,31).

TABLE 7 PCI Versus CABG Hazard Ratios for FREEDOM Primary Outcome of All-Cause Death/Stroke/MI: Time-Dependent Cox Regression Modeling Results*

Group	<2 Yrs Post-Procedure		≥2 Yrs Post-Procedure	
	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
All (n = 1,850)	1.11 (0.85–1.45)	0.44	2.06 (1.41–3.02)	<0.001
ITDM (n = 602)	1.06 (0.70–1,61)	0.78	1.52 (0.86–2.70)	0.15
Non-ITDM (n = 1,248)	1.12 (0.79–1.58)	0.54	2.46 (1.48–4.09)	<0.001

*Treatment group × time period interaction p values = 0.009 for all, 0.32 for ITDM, 0.012 for non-ITDM.

Abbreviations as in Tables 1 and 3.

STUDY LIMITATIONS. The present study was limited by the small stratum sizes for the analyses of outcome by DM status by SYNTAX score; hence, the confidence intervals for the stratum-specific event rates were rather wide. The precise determination of the PCI versus CABG treatment difference in ITDM patients with extensive coronary artery disease can be more

accurately determined in a dedicated, prospective study. In addition, few baseline characteristics differed between ITDM PCI and ITDM CABG subgroups.

CONCLUSIONS

In patients with diabetes and multivessel coronary artery disease, the rate of major adverse cardiovascular events (death, MI, or stroke) is higher in patients treated with insulin than in those not treated with insulin. Furthermore, we did not detect a significant difference in the magnitude of PCI versus CABG treatment effect for patients treated with insulin and those not treated with insulin.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In the FREEDOM trial, CABG was associated with better clinical outcomes than PCI in patients with diabetes and multivessel disease managed with or without insulin. Patients on insulin had higher event rates compared to those not on insulin regardless of revascularization mode.

COMPETENCY IN PATIENT CARE: Consultation with a cardiac surgeon should be obtained before multivessel myocardial revascularization in a patient with diabetes who has angina pectoris or its equivalent.

TRANSLATIONAL OUTLOOK: Adequately powered randomized trials are needed to confirm the superiority of CABG in patients with insulin-dependent diabetes mellitus who have multivessel coronary disease, left main coronary artery disease, or undergo PCI with later-generation drug-eluting stents.

REFERENCES

1. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract 2010;87:4–14.

2. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Diagnosed and Undiagnosed Diabetes among People Ages 20 Years or Older, United States, 2010. Available at: http://diabetes.niddk.nih.gov/dm/pubs/statistics/DM_Statistics_508.pdf. 2011. Accessed August 4, 2014.

3. Wit MA, de Mulder M, Jansen EK, Umans VA. Diabetes mellitus and its impact on long-term outcomes after coronary artery bypass graft surgery. Acta Diabetol 2013;50:123–8.

4. Hillegass WB, Patel MR, Klein LW, et al. Long-term outcomes of older diabetic patients after percutaneous coronary stenting in the United States: a report from the National Cardiovascular Data Registry, 2004 to 2008. J Am Coll Cardiol 2012;60:2280–9.

5. Roffi M, Angiolillo DJ, Kappetein AP. Current concepts on coronary revascularization in diabetic patients. Eur Heart J 2011;32:2748–57.

6. Holper EM, Abbott JD, Mulukutla S, et al. Temporal changes in the outcomes of patients with diabetes mellitus undergoing percutaneous coronary intervention in the National Heart, Lung, and Blood Institute dynamic registry. Am Heart J 2011;161:397–403.e1.

7. Natali A, Vichi S, Landi P, Severi S, L'Abbate A, Ferrannini E. Coronary atherosclerosis in Type II diabetes: angiographic findings and clinical outcome. Diabetologia 2000;43:632–41.

8. Pajunen P, Taskinen MR, Nieminen MS, Syvanne M. Angiographic severity and extent of coronary artery disease in patients with type 1 diabetes mellitus. Am J Cardiol 2000;86:1080–5.

9. Machecourt J, Danchin N, Lablanche JM, et al. Risk factors for stent thrombosis after implantation of sirolimus-eluting stents in diabetic and nondiabetic patients: the EVASTENT Matched-Cohort Registry. J Am Coll Cardiol 2007;50:501–8.

10. Mehran R, Dangas GD, Kobayashi Y, et al. Short- and long-term results after multivessel stenting in diabetic patients. J Am Coll Cardiol 2004;43:1348–54.

11. Farkouh ME, Domanski M, Sleeper LA, et al. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med 2012;367:2375–84.

12. Lazar HL, Fitzgerald C, Gross S, Heeren T, Aldea GS, Shemin RJ. Determinants of length of stay after coronary artery bypass graft surgery. Circulation 1995;92:II120–4.

13. Whang W, Bigger JT Jr., the CABG Patch Trial Investigators and Coordinators. Diabetes and outcomes of coronary artery bypass graft surgery in patients with severe left ventricular dysfunction: results from The CABG Patch Trial database. J Am Coll Cardiol 2000;36:1166–72.

14. Carson JL, Scholz PM, Chen AY, Peterson ED, Gold J, Schneider SH. Diabetes mellitus increases short-term mortality and morbidity in patients undergoing coronary artery bypass graft surgery. J Am Coll Cardiol 2002;40:418–23.

15. Farkouh ME, Dangas G, Leon MB, et al. Design of the Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal management of Multivessel disease (FREEDOM) trial. Am Heart J 2008;155:215–23.

16. Sianos G, Morel MA, Kappetein AP, et al. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention 2005;1:219–27.

17. Kapur A, Hall RJ, Malik IS, et al. Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients. 1-year results of the CARDia (Coronary Artery Revascularization in Diabetes) trial. J Am Coll Cardiol 2010;55:432–40.

18. Kappetein AP, Head SJ, Morice MC, et al. Treatment of complex coronary artery disease in patients with diabetes: 5-year results comparing outcomes of bypass surgery and percutaneous coronary intervention in the SYNTAX trial. Eur J Cardiothorac Surg 2013;43:1006–13.

19. Verma S, Farkouh ME, Yanagawa B, et al. Comparison of coronary artery bypass surgery and percutaneous coronary intervention in patients with diabetes: a meta-analysis of randomised controlled trials. Lancet Diabetes Endocrinol 2013;1:317–28.

20. Palmerini T, Biondi-Zoccai G, Reggiani LB, et al. Risk of stroke with coronary artery bypass graft surgery compared with percutaneous coronary intervention. J Am Coll Cardiol 2012;60:798–805.

21. Muniyappa R, Montagnani M, Koh KK, Quon MJ. Cardiovascular actions of insulin. Endocr Rev 2007;28:463–91.

22. Potenza MA, Addabbo F, Montagnani M. Vascular actions of insulin with implications for

endothelial dysfunction. Am J Physiol Endocrinol Metab 2009;297:E568–77.

23. Wang MY, Yu X, Lee Y, et al. Iatrogenic hyperinsulinemia in type 1 diabetes: its effect on atherogenic risk markers. J Diabetes Complications 2013;27:70–4.

24. Garcia-Puig J, Ruilope LM, Luque M, Fernandez J, Ortega R, Dal-Re R, AVANT Study Group Investigators. Glucose metabolism in patients with essential hypertension. Am J Med 2006;119:318–26.

25. Shimizu I, Minamino T, Toko H, et al. Excessive cardiac insulin signaling exacerbates systolic dysfunction induced by pressure overload in rodents. J Clin Invest 2010;120:1506–14.

26. Shiojima I, Sato K, Izumiya Y, et al. Disruption of coordinated cardiac hypertrophy and angiogenesis contributes to the transition to heart failure. J Clin Invest 2005;115:2108–18.

27. Fang ZY, Prins JB, Marwick TH. Diabetic cardiomyopathy: evidence, mechanisms, and therapeutic implications. Endocr Rev 2004;25:543–67.

28. Ingelsson E, Sundstrom J, Arnlov J, Zethelius B, Lind L. Insulin resistance and risk of congestive heart failure. JAMA 2005;294:334–41.

29. Swan JW, Anker SD, Walton C, et al. Insulin resistance in chronic heart failure: relation to severity and etiology of heart failure. J Am Coll Cardiol 1997;30:527–32.

30. Biondi-Zoccai GGL, Abbate A, Liuzzo G, Biasucci LM. Atherothrombosis, inflammation, and diabetes. J Am Coll Cardiol 2003;41:1071–7.

31. Creager MA, Lüscher TF, Cosentino F, Beckman JA. Diabetes and vascular disease: pathophysiology, clinical consequences, and medical therapy: part I. Circulation 2003;108:1527–32.

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APPENDIX For supplemental figures and tables, and a list of the other FREEDOM trial investigators, please see the online version of this article.