Original Investigation

Quality of Life After PCI vs CABG Among Patients With Diabetes and Multivessel Coronary Artery Disease
A Randomized Clinical Trial

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IMPORTANCE The FREEDOM trial demonstrated that among patients with diabetes mellitus and multivessel coronary artery disease, coronary artery bypass graft (CABG) surgery resulted in lower rates of death and myocardial infarction but a higher risk of stroke when compared with percutaneous coronary intervention (PCI) using drug-eluting stents. Whether there are treatment differences in health status, as assessed from the patient's perspective, is unknown.

OBJECTIVES To compare the relative effects of CABG vs PCI using drug-eluting stents on health status among patients with diabetes mellitus and multivessel coronary artery disease.

DESIGN, SETTING, AND PARTICIPANTS Between 2005 and 2010, 1900 patients from 18 countries with diabetes mellitus and multivessel coronary artery disease were randomized to undergo either CABG surgery (n = 947) or PCI (n = 953) as an initial treatment strategy. Of these, a total of 1880 patients had baseline health status assessed (935 CABG, 945 PCI) and comprised the primary analytic sample.

INTERVENTIONS Initial revascularization with CABG surgery or PCI.

MAIN OUTCOMES AND MEASURES Health status was assessed using the angina frequency, physical limitations, and quality-of-life domains of the Seattle Angina Questionnaire at baseline, at 1, 6, and 12 months, and annually thereafter. For each scale, scores range from 0 to 100 with higher scores representing better health. The effect of CABG surgery vs PCI was evaluated using longitudinal mixed-effect models.

RESULTS At baseline, mean (SD) scores for the angina frequency, physical limitations, and quality-of-life subscales of the Seattle Angina Questionnaire were 70.9 (25.1), 67.3 (24.4), and 47.8 (25.0) for the CABG group and 71.4 (24.7), 69.9 (23.2), and 49.2 (25.7) for the PCI group, respectively. At 2-year follow-up, mean (SD) scores were 96.0 (11.9), 87.8 (18.7), and 82.2 (18.9) after CABG and 94.7 (14.3), 86.0 (19.3), and 80.4 (19.6) after PCI, with significantly greater benefit of CABG on each domain (mean treatment benefit, 1.3 [95% CI, 0.3-2.2], 4.4 [95% CI, 2.7-6.1], and 2.2 [95% CI, 0.7-3.8] points, respectively; $P < .01$ for each comparison). Beyond 2 years, the 2 revascularization strategies provided generally similar patient-reported outcomes.

CONCLUSIONS AND RELEVANCE For patients with diabetes and multivessel CAD, CABG surgery provided slightly better intermediate-term health status and quality of life than PCI using drug-eluting stents. The magnitude of benefit was small, without consistent differences beyond 2 years, in part due to the higher rate of repeat revascularization with PCI.

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Although previous studies have demonstrated that coronary artery bypass graft (CABG) surgery is generally preferred over percutaneous coronary intervention (PCI) for patients with diabetes mellitus and multivessel coronary artery disease, these studies were based largely on data from the balloon angioplasty or bare metal stent eras.[1-3] Recently, the FREEDOM trial (Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease) demonstrated that the benefits of CABG also extend to patients treated with drug-eluting stents and contemporary medical therapy.[4] In addition to providing benefit in the overall population, CABG demonstrated consistent results across all major subgroups, and formal cost-effectiveness analysis demonstrated that CABG was an economically attractive strategy from a societal perspective as well.[4,5]

Despite these benefits across a broad range of relevant outcomes and clinical subgroups, it is not clear whether CABG should be recommended over PCI using drug-eluting stents for all patients with diabetes mellitus and multivessel coronary artery disease. Although the benefits of CABG in FREEDOM were driven by significant reductions in all-cause mortality ($P = .049$) as well as myocardial infarction ($P < .001$), the mortality benefit did not emerge until 4 to 5 years after initial treatment. Moreover, consistent with other contemporary studies,[6,7] rates of stroke were significantly higher after CABG than PCI. In addition, the longer recovery period after CABG vs PCI may be particularly relevant to patients who are more concerned about quality rather than duration of life.[8,9] To provide a more complete picture of the risks and benefits of these alternative revascularization strategies in patients with diabetes, it is important to assess outcomes directly from the patients' perspective including symptoms, functional status, and quality of life. Accordingly, we designed and implemented a prospective health status substudy alongside the FREEDOM trial.

Methods

Study Design

The design, methods, and clinical and economic results of the FREEDOM trial have been described previously.[4,5,10] Briefly, between April 2005 and April 2010, patients from 18 countries with diabetes mellitus and angiographically confirmed multivessel coronary artery disease were randomized on a 1:1 basis to undergo revascularization by either CABG or PCI using drug-eluting stents. All patients had an indication for revascularization and were suitable candidates for both procedures. All procedures were performed using standard techniques. Following revascularization, optimal medical therapy was recommended for both groups including tight control of diabetes mellitus, hypertension, and dyslipidemia. Institutional review board approval of the protocol was obtained at all sites and all patients provided written informed consent.

Health Status Assessment

Health status assessments were performed using standardized, written questionnaires administered to each patient at baseline (prior to randomization), at 1, 6, and 12 months post-randomization, and annually thereafter. In general, questionnaires were administered in person at the time of scheduled follow-up visits. If patients did not complete the questionnaire at that time, it was administered by mail. Questionnaires were administered using linguistically and culturally validated translations in each patient's native language.[11,12]

Disease-specific health status was assessed using the Seattle Angina Questionnaire (SAQ) and the Rose Dyspnea Scale (RDS).[13-16] The SAQ is a validated and reliable 19-item questionnaire that measures coronary artery disease–related health status across 5 domains. Scores range from 0 to 100 for each domain with higher scores denoting better health status and fewer symptoms. The SAQ has undergone extensive reliability and validity testing and has been shown to correlate with long-term survival and hospitalization for an acute coronary syndrome among patients with chronic coronary artery disease.[13,14,17] In order to reduce respondent burden and to focus on those aspects of health status most likely to capture treatment-related differences, data were collected for 3 of the 5 SAQ domains: angina frequency, physical limitation, and quality of life. Previous studies have suggested that differences of 8 to 10 points are clinically meaningful for each of the SAQ subscales.[10]

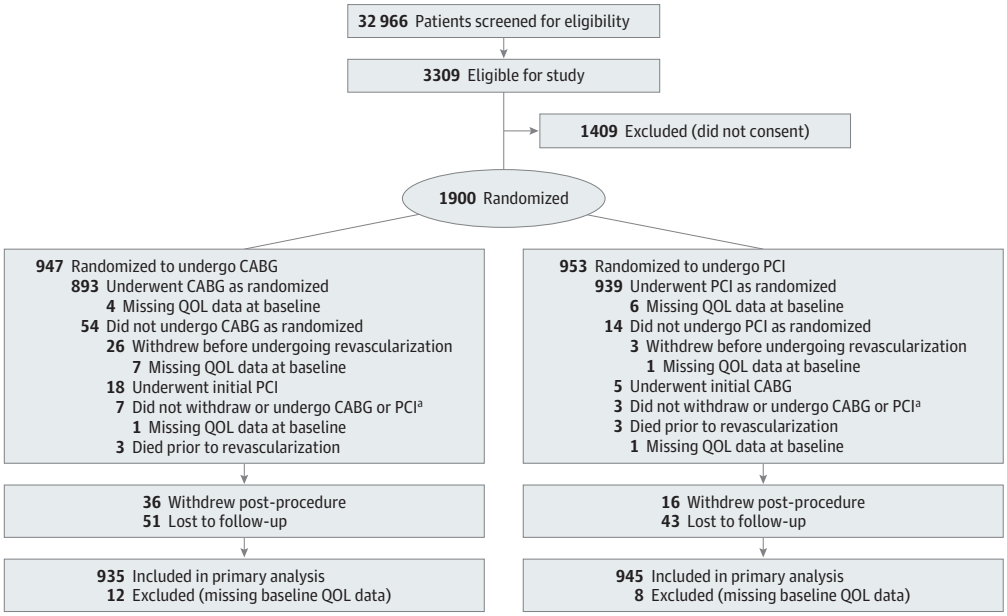
The RDS is a 4-item questionnaire that assesses a patient's level of breathlessness with common activities. Scores range from 0 to 4, with 0 indicating no dyspnea with activities and 4 indicating that dyspnea occurs with minimal physical activity (eg, dressing). Previous studies among patients with an acute coronary syndrome have demonstrated the RDS scale to have acceptable reliability, responsiveness, and internal validity as a measure of health status.[15,18] In addition, higher RDS scores correlate with a higher risk of rehospitalization and long-term mortality in this population.[19]

Statistical Analysis

Unless otherwise specified, the analytic population for this study consisted of all randomized patients with available baseline health status data. Intention-to-treat analysis was used to study this population. When indicated, secondary analyses were performed using a per-protocol approach in which only patients who underwent their assigned revascularization procedure were included. Baseline characteristics were compared between the 2 groups using *t* tests for continuous variables and χ^2 tests for categorical variables. Mean health status scores were compared between groups at each time point by means of longitudinal random-effect growth-curve models. These models incorporate all available health status scores including those for patients who subsequently died, withdrew from the study, or were lost to follow-up, and assume that any missing data are missing at random.[20] Variables included in the growth curve models included the baseline score of the health status domain being assessed, treatment assignment, and follow-up time. Linear, quadratic, and cubic effects of time were considered, as well as all corresponding interactions between treatment and time. The models were optimized using a backward elimination procedure, starting with the highest order of time × treatment interaction.

In addition to analyzing the SAQ scores as continuous variables, we performed secondary analyses in which the SAQ-

Figure 1. Patient Flow for the FREEDOM Trial



Patients included in the primary analysis indicate the primary analytic population for the quality-of-life (QOL) study.
[a]Patients who did not die, withdraw, or undergo coronary artery bypass graft (CABG) surgery or percutaneous coronary intervention (PCI) remained in the study but did not undergo revascularization.

angina frequency scale was treated as an ordinal variable, with patients classified as being angina free (score of 100), or having angina either monthly (score of 70-90), weekly (score of 40-60), or daily (score of ≤30 [scores are reported by increments of 10]). The effect of treatment with CABG vs PCI on this categorical outcome variable at each follow-up time point was analyzed using ordinal logistic regression. A similar approach was applied to the RDS. Additional analyses of both the SAQ and RDS were performed using this approach while incorporating death as the worst possible health state on the ordinal scale.

The extent to which the effect of CABG vs PCI on the SAQ-angina frequency scale differed according to subgroups was examined through the addition of treatment × subgroup × time interaction terms to the longitudinal models. All subgroup analyses were prespecified and considered the following factors: age (<65 vs 65-75 vs >75 years), sex, number of diseased vessels, involvement of the left anterior descending artery (>70% stenosis), SYNTAX score[21] (≤22 vs 23-32 vs ≥33), and baseline angina severity (daily or weekly vs monthly vs none). These subgroup comparisons were restricted to the 1- and 2-year time points because of increased administrative censoring beyond 2 years and because the greatest overall treatment effect in the main analysis occurred at the 1- and 2-year follow-up time points.

All tests of statistical significance were 2-tailed, and *P* values of less than .05 were considered to indicate statistical significance without adjustment for multiple comparisons. All analyses were performed using SAS for Windows, version 9.3 (SAS Institute Inc).

Results

Patient Population

A total of 1900 patients were randomized to undergo either CABG (n = 947) or PCI (n = 953) as an initial treatment strategy. Of these, 20 patients (12 CABG, 8 PCI) did not have baseline health status data available and were excluded from the analysis (**Figure 1**). There were no significant differences in clinical characteristics between patients with vs without baseline health status data other than in the prevalence of stroke (15.0% [3 of 20] vs 3.3% [62 of 1880]; *P* = .03). Of the 1880 patients in the analytic population, 38 withdrew from the trial or died prior to revascularization (31 patients randomized to CABG and 7 patients to PCI). Among the patients assigned to CABG, 18 crossed over and underwent initial PCI, while 5 patients assigned to initial PCI underwent CABG instead.

Baseline characteristics including health status measures were well matched between the 2 treatment groups (**Table 1**). The mean age was 63 years, and 72% were men. Three-vessel coronary artery disease was present in more than 83% of the population and more than 92% had left anterior descending artery involvement. At baseline, both groups of patients reported significant health status limitations attributable to coronary artery disease. Approximately 35% of patients reported daily or weekly angina prior to randomization, and 25% of patients reported moderate or severe dyspnea at baseline (RDS score ≥3). Median follow-up time was 44 months (interquartile range [IQR], 30-59

Table 1. Baseline Patient Characteristics[a]

Characteristics	PCI (n = 945)	CABG (n = 935)	*P* Value
Sociodemographic			
Age, mean (SD), y	63.2 (8.9)	63.0 (9.2)	.76
Age categories, y			
<65	536 (57.0)	530 (56.1)	.12
65-75	299 (32.0)	335 (35.4)	
>75	100 (10.7)	80 (8.5)	
Male sex	692 (73.2)	653 (69.8)	.10
White race	490 (51.9)	475 (50.8)	.65
Clinical			
Prior myocardial infarction	249 (26.3)	235 (25.1)	.55
History of CHF	240 (25.4)	263 (28.1)	.18
Current smoker	141 (14.9)	156 (16.7)	.30
Peripheral vascular disease	95 (10.1)	98 (10.5)	.76
Prior stroke	37 (3.9)	25 (2.7)	.13
COPD	32 (3.4)	51 (5.5)	.03
Angiographic[b]			
Left anterior descending artery involvement, No./total No. (%)	854/941 (90.8)	867/927 (93.5)	.03
3-vessel disease, No./total No. (%)	772/940 (82.1)	781/927 (84.3)	.22
SYNTAX score, mean (SD)	26.2 (8.4)	26.1 (8.8)	.86
SYNTAX score category, No./total No. (%)			
≤22	326/941 (34.6)	333/926 (36.0)	.49
23-32	435/941 (46.2)	403/926 (43.5)	
≥33	180/941 (19.1)	190/926 (20.5)	
Quality of life			
SAQ, mean (SD)[c]			
Angina frequency	71.4 (24.7)	70.9 (25.1)	.68
Physical limitations	69.9 (23.2)	67.3 (24.4)	.02
Quality of life	49.2 (25.7)	47.8 (25.0)	.23
SAQ-angina frequency category, No./total No. (%)			
Daily	88/944 (9.3)	91/935 (9.7)	.36
Weekly	264/944 (28.0)	246/935 (26.3)	
Monthly	368/944 (39.0)	398/935 (42.6)	
None	224/944 (23.7)	200/935 (21.4)	
RDS, No./total No. (%)[d]			
0	280/944 (29.7)	285/932 (30.6)	.99
1	213/944 (22.6)	203/932 (21.8)	
2	206/944 (21.8)	204/932 (21.9)	
3	134/944 (14.2)	133/932 (14.3)	
4	111/944 (11.8)	107/932 (11.5)	

Abbreviations: CABG, coronary artery bypass graft; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; RDS, Rose Dyspnea Scale; SAQ, Seattle Angina Questionnaire.

[a] Data are reported as No. (%) unless otherwise indicated.

[b] Denominators may not match for some variables due to missing baseline data.

[c] Scores on the SAQ scale (reported by increments of 10) range from 0 to 100 with higher scores indicating better quality of life. Zero indicates daily angina or nitroglycerin use, severely limited physical activity due to cardiac disease, or severely affected quality of life for each domain. A score of 100 indicates no limitations on the same subscales.

[d] RDS scores range from 0 to 4 with higher scores indicating increased dyspnea-related limitations (0, no dyspnea with activities; 4, dyspnea occurs with minimal physical activity like getting dressed).

months) for the CABG group and 47 months (IQR, 31-59 months) for the PCI group.

Use of Antianginal Medications

The use of antianginal medications at each follow-up time point is summarized in eTable 1 in the Supplement. β-Blockers were used in approximately 80% of patients at almost all time points and did not differ between the 2 groups. The use of calcium channel blockers and long-acting nitrates was much less frequent overall, but tended to be higher after PCI than after CABG, with absolute differences ranging from 0.7% to 10.3% over time.

Health Status Outcomes

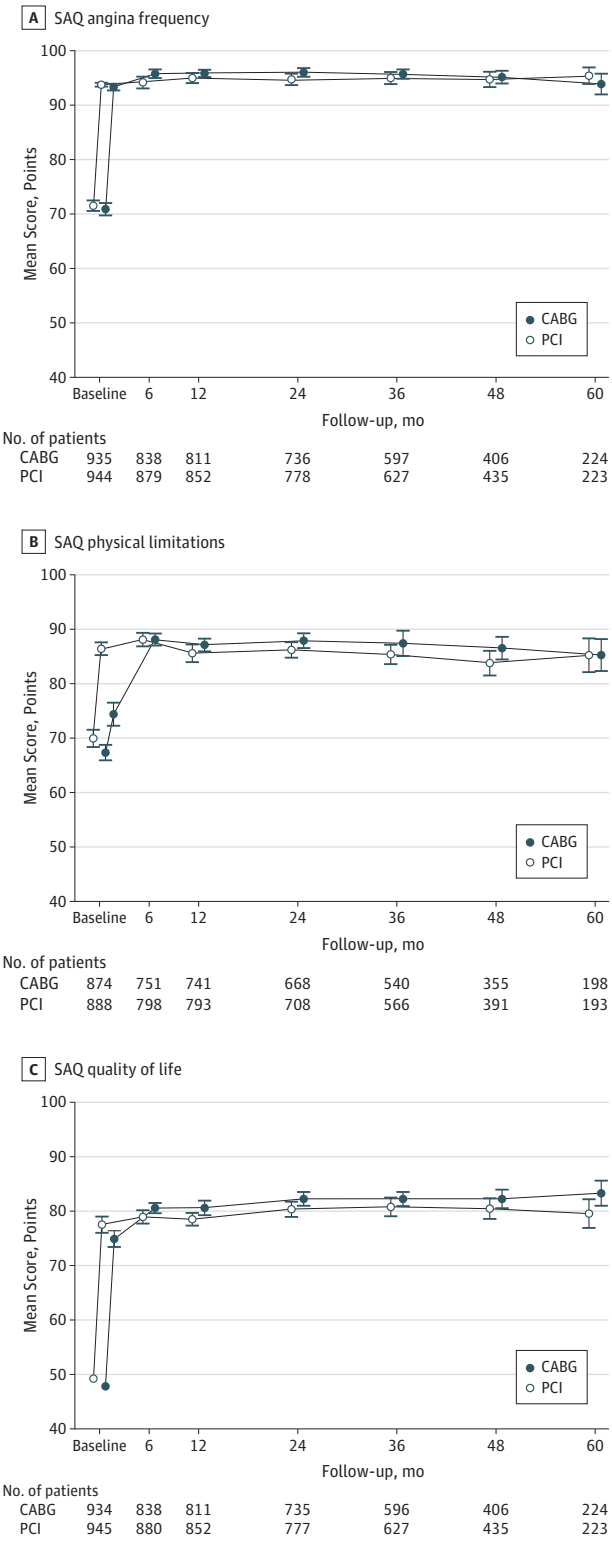
The overall questionnaire response rate was more than 80% for eligible patients during the first 3 years of follow-up and more than 70% in years 4 and 5 (eTable 2 in the Supplement). Compared with baseline, both groups demonstrated substantial improvement in the SAQ-angina frequency subscale that was apparent by 1 month and sustained throughout the 5-year follow-up period (**Figure 2**A and eTable 3 in the Supplement). Between-group comparisons demonstrated that CABG resulted in slightly higher scores than PCI on the SAQ-angina frequency subscale at the 1-year (mean difference, 1.0) and 2-year (mean difference, 1.3) follow-up time points (**Table 2**). By 3

years, however, there was no significant difference in angina relief between the PCI and CABG groups. When analyzed as a categorical variable, the proportion of angina-free patients tended to be slightly greater with CABG than with PCI at 6 months (83.7% vs 78.1%), 12 months (83.5% vs 79.5), and 24 months (83.3% vs 81.0%), although the differences were only statistically significant at 6 and 12 months (**Figure 3** and eTable 4 in the Supplement). When death was included as the worst possible health state in the ordinal analysis, CABG remained superior to PCI at 6 and 12 months, but there were no significant differences at any of the later time points (eTable 5 in the Supplement).

The results for the SAQ-physical limitation and SAQ-quality-of-life subscales are summarized in Figure 2B and Figure 2C, respectively (and in eTable 3 in the Supplement). Both treatment groups demonstrated substantial and sustained improvement in these subscales compared with baseline, yet the temporal pattern and extent of improvement differed by treatment strategy. At 1 month, PCI resulted in greater improvement compared with CABG for both the physical limitations (mean difference between CABG and PCI, −8.1 points; 95% CI, −9.9 to −6.3; $P < .001$) and quality-of-life (mean difference between CABG and PCI, −1.9 points; 95% CI, −3.6 to −0.2; $P = .03$) subscales. By 6 months, scores for the SAQ-quality-of-life subscale were similar for the 2 treatment groups but remained modestly higher with PCI for the physical limitations subscale (mean difference between CABG and PCI, −2.3 points; 95% CI, −3.8 to −0.9; $P = .002$). By 1 year, however, scores were higher with CABG for physical limitations (mean difference between CABG and PCI, 2.0 points; 95% CI, 0.4-3.6; $P = .01$) and quality-of-life subscales (mean difference between CABG and PCI, 1.9 points; 95% CI, 0.4-3.4; $P = .01$). CABG continued to demonstrate better outcomes on the physical limitations and quality-of-life SAQ subscales through 2 and 3 years of follow-up. Beyond year 3, there were no consistent between-group differences for any of the SAQ subscales (although there were significant differences in favor of CABG at 5 years for the physical limitations and quality-of-life subscales). According to longitudinal growth curve analysis, independent predictors of angina frequency at 1 year follow-up included baseline angina frequency, male sex, and the occurrence of repeat revascularization during follow-up (inverse association). After adjustment for these factors, treatment group was no longer associated with the SAQ-angina frequency score. Other complications, including myocardial infarction and stroke, were not associated with follow-up health status according to the SAQ subscales.

Results for the RDS are summarized in **Figure 4** (and in eTable 6 in the Supplement). Both CABG and PCI resulted in substantial reductions in the level of dyspnea over time, but the rate of improvement was more rapid with PCI. At 1 month, PCI patients were more likely to be free of limitations due to dyspnea than patients randomized to CABG (RDS 0: 67.6% vs 58.0%; $P < .001$). These between-group differences were no longer apparent by 6 months (65.2% vs 66.9%; $P = .99$). Whereas 25% of patients had moderate to severe dyspnea (RDS 3 or 4) at baseline, by 12 months, these proportions had fallen to 9.1% for both groups, and remained between 10 and 12% throughout the follow-up period.

Figure 2. Seattle Angina Questionnaire Results



Mean scores are reported (error bars indicate 95% CIs) for the angina frequency, physical limitation, and quality-of-life subscales of the Seattle Angina Questionnaire (SAQ). Scores for each subscale range from 0 to 100 (reported by increments of 10) with higher scores representing better health status or quality of life.

Subgroup Analysis

The estimated effect of CABG vs PCI on the SAQ-angina frequency scale at 1- and 2-year follow-up within prespecified subgroups is summarized in **Figure 5**A and Figure 5B, respectively. There was no evidence of significant heterogeneity in terms of the effect of CABG vs PCI using drug-eluting stents across most of the subgroup categories. However there were significant interactions between treatment assignment and both SYNTAX score and baseline angina frequency. At 1-year follow-up, patients with an intermediate SYNTAX score (23-32) demonstrated significantly greater angina relief with CABG than with PCI using drug-eluting stents (mean adjusted difference, 2.79 points) whereas the benefits were minimal for patients with low or high SYNTAX scores (−0.14 and 0.30 points, respectively). CABG was also associated with greater angina relief among patients with daily or weekly angina at baseline (mean adjusted difference, 1.76 points) as compared with patients with only monthly (mean adjusted difference, 1.29 points) or no angina (mean adjusted difference, −0.93 points). Similar patterns were observed at 2-year follow-up as well.

Table 2. Mean Effect of CABG and PCI on Disease-Specific Health Status According to Longitudinal Models Adjusted for Baseline

SAQ Subscale and Time Point, mo	Treatment Difference, CABG vs PCI (95% CI)[a]	*P* Value
Angina frequency		
1	0.3 (−0.7 to 1.4)	.54
6	0.7 (−0.2 to 1.6)	.12
12	1.0 (0.2 to 1.9)	.02
24	1.3 (0.3 to 2.2)	.01
36	1.0 (−0.1 to 2.0)	.07
48	0.2 (−1.1 to 1.5)	.79
60	−1.2 (−3.3 to 0.9)	.28
Physical limitation		
1	−8.1 (−9.9 to −6.3)	<.001
6	−2.3 (−3.8 to −0.9)	.002
12	2.0 (0.4 to 3.6)	.01
24	4.4 (2.7 to 6.1)	<.001
36	2.5 (0.5 to 4.5)	.01
48	1.0 (−1.4 to 3.4)	.42
60	4.6 (0.8 to 8.3)	.02
Quality of life		
1	−1.9 (−3.6 to −0.2)	.03
6	0.4 (−1.1 to 1.8)	.62
12	1.9 (0.4 to 3.4)	.01
24	2.2 (0.7 to 3.8)	.003
36	1.0 (−0.7 to 2.7)	.25
48	0.6 (−1.4 to 2.6)	.57
60	3.4 (0.1 to 6.8)	.04

Abbreviations: CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; SAQ, Seattle Angina Questionnaire.

[a] Positive values indicate better quality of life with CABG.

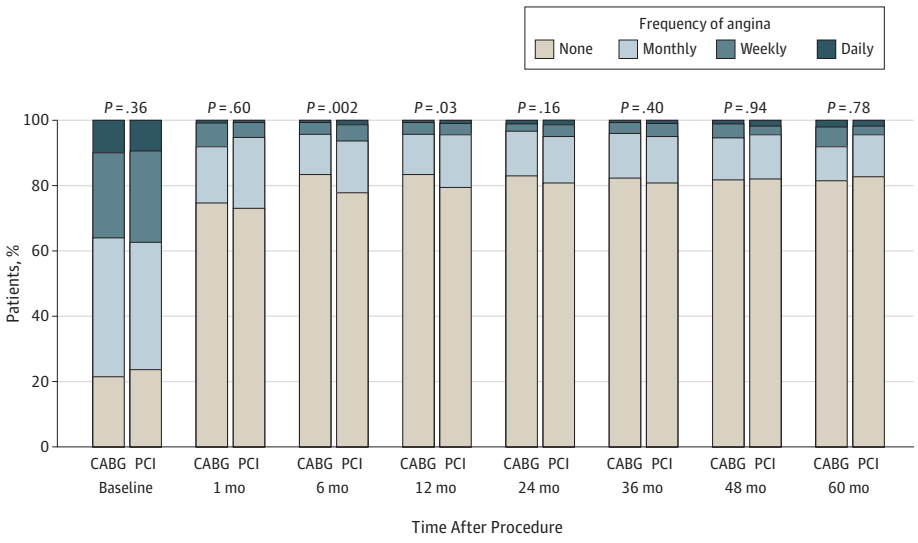
Sensitivity Analyses

There were no major changes when the SAQ and RDS were analyzed using a per-protocol approach rather than an intention to treat one (n = 1819, data not shown). Our results were also similar when the analysis was restricted to patients who had angina at baseline (n = 1476, eTables 7A and 7B in the Supplement) or patients with daily or weekly angina at baseline (n = 710, eTables 8A and 8B in the Supplement). Results were similar when worst-case values were imputed to patients with missing health status data who experienced a nonfatal myocardial infarction or stroke during follow-up (eTable 9 in the Supplement).

Discussion

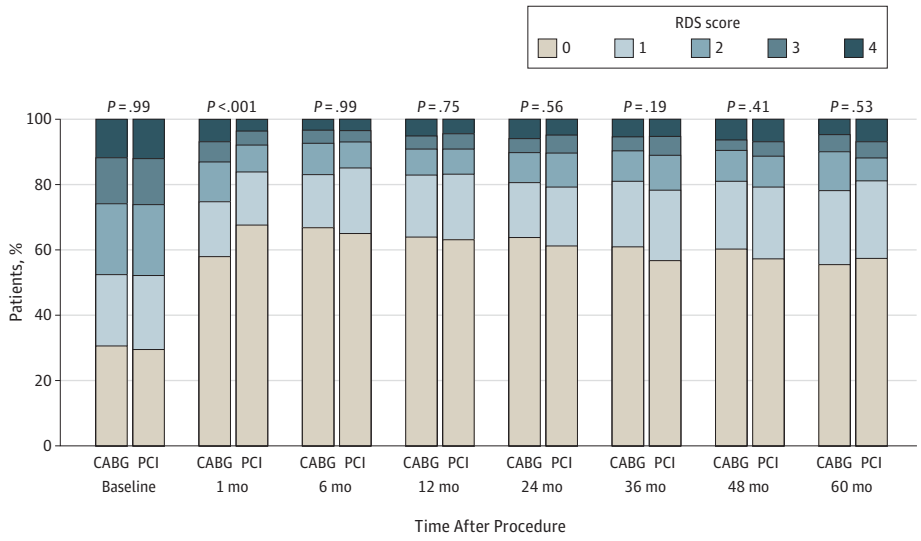
Using data from the FREEDOM trial, we examined long-term health status and quality of life of patients with diabetes mellitus and multivessel coronary artery disease undergoing CABG and PCI using drug-eluting stents. The study demonstrated several important findings.

Figure 3. Frequency of Angina by Treatment Group



Frequency of angina by treatment group according to the Seattle Angina Questionnaire (SAQ)–angina frequency scale. Categories (with scores by increments of 10) were defined as no angina (score, 100), monthly angina (score, 70-90), weekly angina (score, 40-60), or daily angina (score, <40). See eTable 4 in the Supplement for exact data and numbers of patients. *P* value comparisons were determined using ordinal logistic regression.

Figure 4. Frequency of Dyspnea-Related Limitation in Physical Activity



Data are reported according to the Rose Dyspnea Scale (RDS; range, 0-4; higher scores represent more dyspnea). *P* value comparisons were determined using ordinal logistic regression. See eTable 6 in the Supplement for exact data.

First, patients experienced substantial and durable improvements in cardiovascular-specific health status as assessed by both the SAQ (a measure of angina and its effect on patients' physical limitations and quality of life) as well as the RDS (a measure of breathlessness and its effect on patients' physical activity) following both PCI and CABG.

Second, although PCI resulted in more rapid improvement in health status and quality of life compared with CABG, these benefits were transient and largely restricted to the first month of follow-up. Between 6 months and 2 years, health status was slightly better with CABG across a range of cardiac-specific domains including angina relief, physical function, and overall quality of life. Beyond 2 years, there were no consistent differences in any health status or quality-of-life domains between the CABG and PCI strategies.

Third, the intermediate-term benefits of CABG over PCI in terms of angina relief were generally consistent across patient subgroups, although there was a suggestion that these benefits were enhanced among patients with the most severe angina prior to randomization.

Although patients undergoing CABG had less severe angina, more improved physical function, and better quality of life between 6 months and 2 years relative to PCI, these differences were small. Previous studies have suggested that for an individual patient, differences of 8 to 10 points on the SAQ-angina frequency scale would be considered clinically meaningful.[13,14] The mean differences we observed of approximately 1.5 points are well below this level and thus may be less relevant to most patients. The difference between CABG and PCI in FREEDOM is also less than the difference of 3 to 6 points for the comparison of PCI plus optimal medical therapy vs optimal medical therapy alone in the COURAGE trial.[22] When analyzed as a categorical variable, the proportion of patients who were free of any angina was more than 70% with both PCI and CABG at each follow-up time point, and the absolute differences between groups in rates of complete angina relief ranged from 0.5% to 5.6%. Differences between treatment groups in other measures of cardiovascular health including physical limitations, overall quality of life, and breathlessness were similarly small.

Comparison With Previous Studies

Several previous studies have compared the effect of CABG vs PCI on health-related quality of life among patients with multivessel coronary artery disease. In general, these studies have tended to show that compared with PCI, CABG results in superior angina relief over the first 1 to 3 years after initial revascularization.[23] For example, in the BARI (Bypass Angioplasty Revascularization Intervention) trial, which compared balloon angioplasty with CABG, functional status and angina relief were superior over the first 3 years of follow-up with CABG.[24] Similar findings were noted in the RITA (Randomized Intervention Treatment of Angina) trial.[3] Thus, with regard to the timing of benefit, the results of FREEDOM are remarkably similar to previous CABG vs PCI trials.

Conversely, the magnitude of benefit provided by CABG over PCI in the FREEDOM trial was smaller than in many previous PCI vs CABG trials. For example, in the RITA trial, there was a 9.8% absolute difference in the prevalence of angina at 1 year in favor of CABG vs balloon angioplasty.[3] In the BARI trial, the difference in angina relief was even larger with an absolute difference of 15% in the prevalence of angina at 1 year in favor of CABG.[24]

With the introduction of bare metal stents and the accompanying reductions in restenosis,[25-27] the health status benefits of CABG over PCI for patients undergoing multivessel revascularization were diminished but remained clinically meaningful. In the ARTS (Arterial Revascularization Therapies Study) trial, the absolute difference in angina prevalence at 1 year was approximately 10% in favor of CABG and decreased to approximately 5% at 5 years.[2,28] In the SOS (Stent or Surgery) trial, the difference in the SAQ-angina frequency

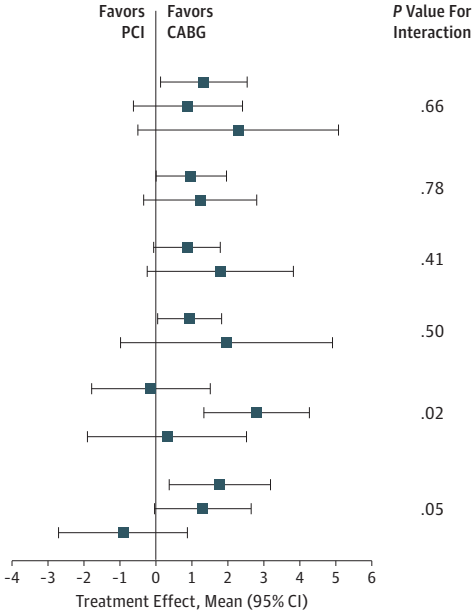
score between PCI (with bare metal stents) and CABG was approximately 6 points at 6-month follow-up and approximately 3 points at 1 year—differences that are nearly twice as large as those observed in the FREEDOM trial.[29]

Conversely, at least in the short term, the difference in angina relief between CABG and PCI observed in FREEDOM is remarkably similar to that seen in the SYNTAX trial,[30] which is the only other randomized trial of multivessel coronary revascu-

Figure 5. Subgroup Analysis of the Mean Treatment Effect of CABG vs PCI on the SAQ–Angina Frequency Subscale

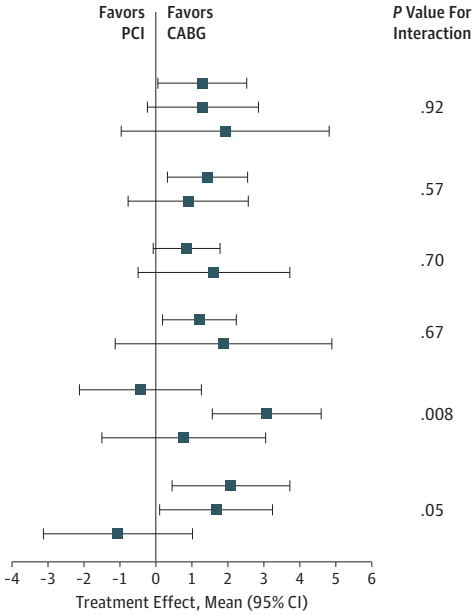
12-Month Treatment Effect

Subgroup	CABG No. of Patients	CABG Score, Mean (95% CI)	PCI No. of Patients	PCI Score, Mean (95% CI)	Mean Treatment Effect (95% CI)	P Value For Interaction
Age, y						
<65	536	95.6 (94.8-96.5)	530	94.3 (93.5-95.2)	1.32 (0.12 to 2.52)	
65-75	299	96.0 (94.9-97.1)	335	95.1 (94.1-96.2)	0.88 (-0.63 to 2.39)	.66
>75	100	96.7 (94.8-98.6)	80	94.4 (92.4-96.5)	2.28 (-0.51 to 5.06)	
Sex						
Men	653	96.0 (95.3-96.8)	692	95.0 (94.3-95.8)	0.97 (-0.02 to 1.95)	.78
Women	252	95.1 (94.0-96.2)	253	93.9 (92.7-95.0)	1.22 (-0.34 to 2.79)	
Diagnosis						
3-Vessel disease	781	95.7 (95.0-96.4)	771	94.9 (94.2-95.6)	0.85 (-0.07 to 1.78)	.41
2-Vessel disease	146	95.9 (94.4-97.4)	168	94.1 (92.7-95.5)	1.78 (-0.25 to 3.80)	
LAD disease						
Yes	867	95.7 (95.0-96.4)	854	94.8 (94.1-95.4)	0.92 (0.04 to 1.81)	.50
No	60	96.2 (94.0-98.5)	87	94.3 (92.4-96.2)	1.95 (-0.99 to 4.89)	
SYNTAX score						
≤22	333	94.9 (93.7-96.1)	326	95.1 (93.9-96.2)	-0.14 (-1.79 to 1.50)	
23-32	403	96.8 (95.7-97.9)	434	94.0 (93.0-95.0)	2.79 (1.32 to 4.25)	.02
≥33	190	95.5 (93.9-97.0)	180	95.2 (93.6-96.7)	0.30 (-1.91 to 2.51)	
Angina frequency						
Daily or weekly	337	93.8 (92.8-94.9)	349	92.1 (91.1-93.1)	1.76 (0.36 to 3.17)	
Monthly	398	96.4 (95.5-97.4)	368	95.2 (94.2-96.1)	1.29 (-0.04 to 2.63)	.05
None	200	97.6 (96.2-98.9)	224	98.5 (97.3-99.7)	-0.93 (-2.71 to 0.86)	



24-Month Treatment Effect

Subgroup	CABG No. of Patients	CABG Score, Mean (95% CI)	PCI No. of Patients	PCI Score, Mean (95% CI)	Mean Treatment Effect (95% CI)	P Value For Interaction
Age, y						
<65	536	96.0 (95.1-96.9)	530	94.7 (93.8-95.6)	1.29 (0.06 to 2.52)	
65-75	299	96.5 (95.3-97.6)	335	95.1 (94.0-96.2)	1.31 (-0.23 to 2.85)	.92
>75	100	97.0 (94.9-99.2)	80	95.1 (92.8-97.4)	1.92 (-0.95 to 4.80)	
Sex						
Men	653	96.7 (95.9-97.5)	692	95.2 (94.5-96.0)	1.43 (0.33 to 2.54)	.57
Women	252	95.0 (93.8-96.2)	253	94.1 (92.9-95.3)	0.90 (-0.76 to 2.56)	
Diagnosis						
3-Vessel disease	781	96.2 (95.5-97.0)	771	95.0 (94.3-95.8)	0.85 (-0.07 to 1.78)	.70
2-Vessel disease	146	96.1 (94.5-97.6)	168	94.5 (93.1-95.9)	1.61 (-0.49 to 3.71)	
LAD disease						
Yes	867	96.2 (95.4-96.9)	854	95.0 (94.2-95.7)	1.21 (0.19 to 2.22)	.67
No	60	96.2 (93.9-98.5)	87	94.3 (92.4-96.3)	1.87 (-1.13 to 4.87)	
SYNTAX score						
≤22	333	95.1 (93.9-96.3)	326	95.5 (94.4-96.7)	-0.43 (-2.12 to 1.26)	
23-32	403	97.3 (96.2-98.4)	434	94.3 (93.2-95.3)	3.07 (1.57 to 4.58)	.008
≥33	190	95.8 (94.2-97.4)	180	95.1 (93.4-96.7)	0.77 (-1.50 to 3.03)	
Angina frequency						
Daily or weekly	337	94.1 (92.9-95.3)	349	92.0 (90.9-93.2)	2.08 (0.45 to 3.71)	
Monthly	398	97.1 (96.0-98.2)	368	95.5 (94.4-96.6)	1.67 (0.12 to 3.23)	.05
None	200	97.8 (96.3-99.3)	224	98.8 (97.4-100.3)	-1.05 (-3.11 to 1.01)	



All subgroup counts are based on the baseline patient assessment. Treatment effects at 12 months, 24 months, associated 95% CIs, and interaction *P* values were derived from longitudinal random-effect growth-curve models. CABG, coronary artery bypass graft; LAD, left anterior descending artery; PCI, percutaneous coronary intervention; SAQ, Seattle Angina Questionnaire.

larization to use drug-eluting stents exclusively. Our results are also consistent with those of the BARI-2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial in which an indirect comparison demonstrated a slightly greater benefit of CABG than PCI on the Duke Activity Status Index (a measure of functional status) when compared with medical therapy.[31]

These trends indirectly suggest that at least some of the quality-of-life benefits of CABG over PCI relate to differences in treatment durability. Although the introduction of drug-eluting stents has clearly reduced the need for repeat revascularization compared with both balloon angioplasty and bare metal stents, even with universal use of drug-eluting stents in FREEDOM, the rate of repeat revascularization was more than twice as high after PCI as compared with CABG. Several previous studies have shown an association between repeat revascularization and impaired health status—particularly around the time of the repeat revascularization procedure.[29,32,33] It is possible that the higher rates of repeat revascularization seen after PCI in FREEDOM mitigated any differences in angina frequency and quality of life between the 2 strategies. Whether further improvements in DES technology would eliminate any health status benefit of CABG over PCI in the diabetic population is unknown.

Clinical Implications

The primary results of the FREEDOM trial demonstrated that for diabetic patients with multivessel coronary artery disease, CABG led to a significant benefit over PCI for the composite endpoint of death, myocardial infarction, or stroke—driven by reductions in both all-cause mortality and myocardial infarction.[4] Although both revascularization strategies led to substantial and sustained improvements in quality of life and functional status in the FREEDOM trial, angina relief was also slightly better with CABG than PCI, especially among patients with the most severe angina at baseline. These findings suggest that CABG should be strongly preferred as the initial revascularization strategy for such patients. Given the increased rate of stroke, as well as the well-recognized longer recovery period with CABG surgery, however, some patients who do not wish to face these acute risks may still choose the less invasive PCI strategy. For such patients, our study provides reassurance that there are not major differences in long-term health status and quality of life between the 2 treatment strategies. Nonetheless, it is important for patients to recognize that the similar late quality-of-life outcomes with PCI and CABG in the FREEDOM trial were achieved with higher rates of antianginal medication use and the need for more frequent repeat revascularization procedures among the PCI group.[34]

Limitations

Our results should be viewed in light of the following limitations. By design, the FREEDOM trial included only a select group of diabetic patients with multivessel disease, such that the results do not necessarily apply to patients who do not meet the trial's inclusion and exclusion criteria. In particular, the results of the FREEDOM trial should not be extrapolated to patients with single-vessel, left-main, or unstable coronary disease.

A second limitation is that health status data were missing for a modest proportion of patients due to a combination of administrative censoring and nonresponse, mainly at the 4- and 5-year time points, and to a greater extent after CABG than PCI. Although our analytic approach accounted for data that were missing at random, results at these later time points might still be affected by informative (ie, nonrandom) censoring and should be interpreted with caution.

A third limitation is that our health status assessment focused on disease-specific, rather than generic measures. Although disease-specific measures are generally more sensitive than generic measures,[13] by focusing on cardiovascular-specific outcomes, it is possible that we underestimated the effect of stroke on patients' overall health status during follow-up, thus biasing our results somewhat in favor of CABG. However, given that absolute differences in rates of stroke were only 2% to 3%, it seems unlikely that generic health status measures would have shown a difference in favor of PCI. Indeed, a previously published comparison of health utility scores from the FREEDOM trial showed no significant difference between the 2 groups except at the 1-month time point.[5] The disease-specific instruments used in this study were also not designed to detect differences in neurocognitive function between the 2 procedures.

The results of the FREEDOM trial only apply to first-generation drug-eluting stents, which were used in the vast majority of PCI procedures in the trial. Although second-generation everolimus-eluting stents have shown lower rates of target lesion revascularization compared with first-generation DES designs in the overall population,[35,36] it is less clear that these benefits apply to diabetic patients.[37]

Conclusions

In summary, these results from the FREEDOM trial demonstrate that for patients with diabetes and multivessel coronary artery disease, both PCI using drug-eluting stents and CABG provided substantial and sustained benefits on cardiovascular-specific health status and quality of life that were evident within 1 month and sustained through 5 years. Between-group comparisons generally favored CABG between 6 months and 2 years, but the observed differences were small. Beyond 2 years, there were no consistent differences between the 2 treatment strategies.

ARTICLE INFORMATION

Author Contributions: Dr Cohen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Spertus, Farkouh, Fuster, Cohen.
Acquisition of data: Wang, Magnuson, Farkouh, Cohen.
Analysis and interpretation of data: Abdallah, Wang, Magnuson, Spertus, Cohen.
Drafting of the manuscript: Abdallah, Wang, Cohen.
Critical revision of the manuscript for important intellectual content: Abdallah, Wang, Magnuson, Spertus, Farkouh, Fuster.
Statistical analysis: Wang, Magnuson.
Obtained funding: Farkouh, Fuster, Cohen.
Administrative, technical, or material support: Farkouh.
Study supervision: Fuster, Cohen.

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