Original Investigation

Effect of Screening for Coronary Artery Disease Using CT Angiography on Mortality and Cardiac Events in High-Risk Patients With Diabetes
The FACTOR-64 Randomized Clinical Trial

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IMPORTANCE Coronary artery disease (CAD) is a major cause of cardiovascular morbidity and mortality in patients with diabetes mellitus, yet CAD often is asymptomatic prior to myocardial infarction (MI) and coronary death.

OBJECTIVE To assess whether routine screening for CAD by coronary computed tomography angiography (CCTA) in patients with type 1 or type 2 diabetes deemed to be at high cardiac risk followed by CCTA-directed therapy would reduce the risk of death and nonfatal coronary outcomes.

DESIGN, SETTING, AND PARTICIPANTS The FACTOR-64 study was a randomized clinical trial in which 900 patients with type 1 or type 2 diabetes of at least 3 to 5 years' duration and without symptoms of CAD were recruited from 45 clinics and practices of a single health system (Intermountain Healthcare, Utah), enrolled at a single-site coordinating center, and randomly assigned to CAD screening with CCTA (n = 452) or to standard national guidelines–based optimal diabetes care (n = 448) (targets: glycated hemoglobin level <7.0%, low-density lipoprotein cholesterol level <100 mg/dL, systolic blood pressure <130 mm Hg). All CCTA imaging was performed at the coordinating center. Standard therapy or aggressive therapy (targets: glycated hemoglobin level <6.0%, low-density lipoprotein cholesterol level <70 mg/dL, high-density lipoprotein cholesterol level >50 mg/dL [women] or >40 mg/dL [men], triglycerides level <150 mg/dL, systolic blood pressure <120 mm Hg), or aggressive therapy with invasive coronary angiography, was recommended based on CCTA findings. Enrollment occurred between July 2007 and May 2013, and follow-up extended to August 2014.

MAIN OUTCOMES AND MEASURES The primary outcome was a composite of all-cause mortality, nonfatal MI, or unstable angina requiring hospitalization; the secondary outcome was ischemic major adverse cardiovascular events (composite of CAD death, nonfatal MI, or unstable angina).

RESULTS At a mean follow-up time of 4.0 (SD, 1.7) years, the primary outcome event rates were not significantly different between the CCTA and the control groups (6.2% [28 events] vs 7.6% [34 events]; hazard ratio, 0.80 [95% CI, 0.49-1.32]; *P* = .38). The incidence of the composite secondary end point of ischemic major adverse cardiovascular events also did not differ between groups (4.4% [20 events] vs 3.8% [17 events]; hazard ratio, 1.15 [95% CI, 0.60-2.19]; *P* = .68).

CONCLUSIONS AND RELEVANCE Among asymptomatic patients with type 1 or type 2 diabetes, use of CCTA to screen for CAD did not reduce the composite rate of all-cause mortality, nonfatal MI, or unstable angina requiring hospitalization at 4 years. These findings do not support CCTA screening in this population.

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Coronary artery disease (CAD) with associated myocardial infarction (MI) is the most common cause of morbidity and mortality in the United States.[1] Often MI is the first symptom of CAD, suggesting the need for more effective screening of high-risk, asymptomatic patients.[1,2]

Diabetes mellitus is the most important CAD risk factor.[3,4] Diabetes mellitus and its precursor, the metabolic syndrome, have become epidemic in the United States.[5] Additionally, patients with diabetes often develop severe but asymptomatic CAD.[6] The combination of aggressive CAD and asymptomatic presentation has made CAD the most common cause of death among patients with diabetes.[5]

In the past, screening for asymptomatic CAD has been limited to noninvasive tests with variable sensitivity and specificity and capable of identifying only obstructive CAD causing myocardial ischemia.[7] The development of high-resolution multidetector coronary computed tomography angiography (CCTA) now provides the opportunity to evaluate the actual coronary anatomy noninvasively and ascertain the overall extent and severity of coronary atherosclerosis.[8] Studies such as CORE 64 (Coronary Artery Evaluation Using 64-Row Multidetector Computed Tomographic Angiography) have demonstrated a high correlation between CCTA and invasive coronary angiography in the determination of CAD extent and severity,[9] resulting in increased clinical utilization of CCTA. However, whether routine CCTA screening in high-risk populations can effect changes in treatment (such as preemptive coronary revascularization or more aggressive medical therapy), leading to a reduction in cardiac events, remains unproven.[2,10-14]

The FACTOR-64 study was a randomized clinical trial that assigned high-risk, asymptomatic patients with diabetes to receive either systematic screening with 64-slice CCTA or standard treatment. The study was performed completely within the Intermountain Healthcare network of hospitals and clinics in the United States. The aim of FACTOR-64 was to test the hypothesis that screening patients with diabetes deemed to be at high risk for the presence of asymptomatic CAD through the use of 64-slice CCTA would result in a significant long-term reduction in death, MI, or hospitalization for unstable angina.

Methods

After approval of the study by the Intermountain Urban Central Region institutional review board, patients with a history of either type 1 or type 2 diabetes mellitus, with no clinical evidence of CAD, who met other eligibility criteria, and who provided personally signed informed consent were enrolled. Inclusion criteria consisted of men 50 years or older or women 55 years or older with diabetes (ie, with documentation of fasting glucose ≥126 mg/dL [6.99 mmol/L] or glycated hemoglobin [HbA_{1c}] level >6.5%) documented for at least 3 years or men 40 years or older or women 45 years or older with diabetes for at least 5 years, with use of antidiabetic medication for at least 1 year prior to enrollment (study protocol available in Supplement 1).

Exclusions included any documented atherosclerotic cardiovascular disease (known CAD [coronary stenosis ≥70%], history of MI, or angina; history of stroke, transient ischemic attack, or carotid or cerebral artery revascularization; or history of claudication, amputation, or peripheral [including renal artery] arterial revascularization); treatment with an investigational drug within 30 days; therapy or condition posing a risk for adherence to study requirements; pregnancy, lactation, or childbearing potential without effective contraception; or limited life expectancy or comorbidity making primary screening and treatment inappropriate.

Baseline clinical and laboratory characteristics were obtained for each participating patient at enrollment. Patient characteristics noted included age; sex; type of diabetes; years diagnosed as having diabetes; race/ethnicity (as self-reported in the medical record); height; weight; blood pressure; smoking history; levels of HbA_{1c}, creatinine, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides; hypertension; hyperlipidemia; all patient-reported medications; family history of diabetes or cardiovascular disease; and comorbidities (based on clinical *International Classification of Diseases, Ninth Revision* diagnosis). Any further laboratory tests were performed only as clinically indicated.

Patients were randomized 1:1 to the screening or no screening groups using a permuted-block randomization scheme.

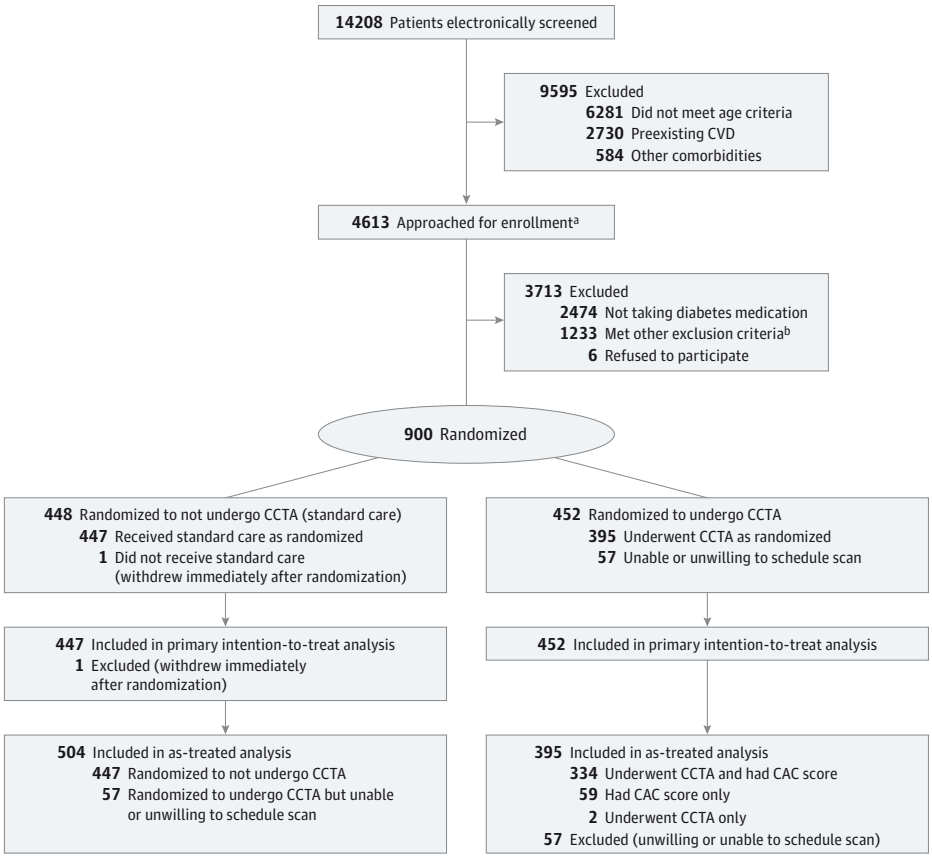
Patient Management

Patients randomized to the screening group underwent CCTA screening as detailed in **Figure 1**. Imaging was performed on a single 64-slice coronary computed tomography (CT) scanner (Aquilion 64, Toshiba America Medical Systems) at Intermountain Medical Center using a standardized protocol.[15] Coronary artery calcium (CAC) levels were obtained from noncontrast-enhanced scans using 3 mm of collimation at a 3-mm slice increment and were scored by the Agatston method. Coronary computed tomography angiography was performed with retrospective gating at 120kV and 350 to 600 mA, with a gantry rotation time of 400 milliseconds. Heart rate was controlled to less than 60/min with oral and, if necessary, intravenous metoprolol. Vasodilation was achieved with sublingual nitroglycerin (0.4 mg). Iopamidol 370 contrast (Isovue, Bracco Diagnostics) was injected into the right antecubital vein with automated bolus tracking at 180 Hounsfield units. Reconstruction using phaseXact software was performed using the FC43 "regular" kernel at 75% of the R-R interval. If phase was not optimal for image analysis, subsequent data sets were reconstructed based on an operator-determined phase of the R-R interval. Mean effective dose was 12 (SD, 2) mSv for CCTA.

If the serum creatinine level was 2.0 mg/dL or greater for men or 1.8 mg/dL or greater for women (to convert to µmol/L, multiply by 88.4), or if some other contraindication (including contrast allergy or inability to reduce heart rate to <60/min) to performing CCTA was present, screening was performed without contrast, and only a CAC score was obtained. All patients randomized to CCTA were strongly encouraged to undergo the protocol scan, even if they could only qualify for CAC scoring.

After completion of the scans, the studies were interpreted by a credentialed physician, and results were entered

Figure 1. Flow of the FACTOR-64 Randomized Clinical Trial



CAC indicates coronary artery calcium; CCTA, coronary computed tomography angiography; CVD, cardiovascular disease.

[a] Approached using letters with follow-up telephone calls (n = 3731) or other methods (n = 882).

[b] For example, diabetes diagnosis of too short duration, other comorbidities, unable to be contacted.

into the medical record. Scan results were divided into 4 prespecified categories based on CAD severity by CCTA or CAC score (severe stenosis: ≥70% stenosis in at least 1 major proximal or large coronary artery; moderate stenosis: 50%-69% stenosis or CAC score >100; mild stenosis: 10%-49% stenosis in any coronary artery or CAC score >10-100; normal: <10% stenosis and minimal or no evidence of plaque and CAC score ≤10).

A recommendation for subsequent management, based on these categories, was communicated to each patient's personal physician. Patients with severe stenosis were recommended to undergo diagnostic coronary angiography. Patients with moderate stenosis were recommended to receive stress cardiac imaging using adenosine or regadenoson cardiac magnetic resonance imaging if possible (otherwise, stress myocardial perfusion imaging and to proceed to invasive diagnostic coronary angiography if clinically relevant myocardial ischemia was detected. For patients with mild stenosis or normal coronary arteries, no further imaging studies were recommended. A recommendation for revascularization by percutaneous coronary intervention or coronary artery bypass graft (CABG) surgery was based on best clinical judgment of the treating physicians.

Information also was collected throughout the study on non-protocol-related cardiac stress or noninvasive imaging testing, coronary angiography, percutaneous coronary intervention, and CABG surgery.

Medical Management

Patients randomized to the control group continued to be treated by their primary care physicians, with the recommendation that they follow the guidelines for standard appropriate diabetes care, which comprised the treatment targets recommended by Intermountain Healthcare's Diabetes Prevention and Management Development Team. These included HbA_{1C} level less than 7.0%, LDL-C level less than 100 mg/dL (to convert to mmol/L, multiply by 0.0259), and systolic blood pressure less than 130 mm Hg (eFigure 1 in Supplement 2).

Patients randomized to CCTA screening received medical management recommendations based on the results of their CT scans. Patients with normal coronary arteries were recommended to continue standard diabetes mellitus care. Patients with mild proximal disease to severe proximal or distal CAD by CCTA or a CAC score greater than 10 were recommended to begin aggressive care to reduce risk factors. This included emphasizing diet and exercise and treatment targets of included LDL-C level less than 70 mg/dL, HDL-C level greater than 50 mg/dL (to convert to mmol/L, multiply by 0.0259), triglyceride level less than 150 mg/dL (to convert to mmol/L, multiply by 0.0113), HbA_{1C} level less than 6.0%, and systolic blood pressure less than 120 mm Hg (eFigure 1 in Supplement 2). After the results of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial[16] were reported, the HbA_{1c} target was no longer emphasized.

Enrollment and Follow-up Evaluations

Enrollment began on July 9, 2007, and ended May 16, 2013, and all patients received follow-up until August 1, 2014. Telephone follow-up was performed for each enrollee biannually for 2 years and then annually thereafter. Outcomes were ascertained by directly questioning the patient (or family if needed), reviewing medical records and querying Intermountain Healthcare electronic health records, and searching the national Social Security Death Index and the Utah State Death Certificate Database. Follow-up lipids panel and HbA_{1c} results were based on routine clinical laboratory results obtained closest to 1 year after randomization. Three patients in the CCTA group and 6 in the control group were lost to telephone follow-up. However, their outcomes were still tracked through the other means described above.

Cardiovascular Events, Sample Size, and Power Estimates

The primary end point was the composite of all-cause mortality, nonfatal MI, or hospitalization for unstable angina after a minimum of 2 years of follow-up. Secondary end points included cardiovascular death (including death attributable to CAD, heart failure, arrhythmia, or sudden cardiac death), alone and together with MI and unstable angina; CAD death, alone and together with MI and unstable angina (ischemic major adverse cardiovascular events); hospitalization for heart failure, worsening renal failure (ie, progression of serum creatinine level by ≥0.5 mg/dL at 30 days and persisting at 1 year), a stroke or carotid revascularization procedure, and a limb amputation or peripheral vascular revascularization procedure.

Based on a 2006 internal study, we estimated a 2-year event rate for all-cause death, MI, or unstable angina of 12.1% for a general population with diabetes and of 16% with our restricted inclusion criteria. We estimated that enrollment of 1100 patients (550 per group) would provide 90% power to detect a 40% reduction in events at a 2-sided α of .05, with 964 participants providing 80% power. Because of longer than expected enrollment time, enrollment was stopped at 900 patients—but with extended follow-up until August 1, 2014 (mean, 4 years), the power to detect a 40% difference between groups remained adequate to determine significance.

Other Prespecified and Post Hoc Analyses

Prespecified analyses of the effects of randomization to the CCTA group on the levels of HbA_{1C}, blood pressure, and fasting lipid panel values after 1 year of follow-up were performed. Additionally, post hoc analyses were performed to assess the effect CCTA scanning had on the use of diagnostic and therapeutic procedures, the association between CCTA-identified levels of coronary artery plaque burden and cardiovascular risk, and the association between subgroups (based on major baseline characteristics and calculated Framingham risk score[17]) and the primary outcome.

Statistical Analysis

Baseline characteristics were described using frequencies and proportions for categorical variables and means and standard deviations, or medians and interquartile ranges, for continuous variables. Bivariable associations between randomization status and baseline characteristics were assessed using nonparametric tests (Wilcoxon rank sum or Kruskal-Wallis). Pairwise changes from baseline to 1-year follow-up lipid levels, HbA_{1C} values, and blood pressure were tested using paired *t* tests, and intergroup assessment was performed using nonparametric tests. Cox proportional hazards regression (with time to first event) was used to estimate hazard ratios (HRs) comparing (1) events by intention-to-treat in CCTA vs control (non-CCTA) patients; and (2) events in patients who actually received the screening CT scan vs those who did not (as-treated analysis). Censoring was done at last date of death certificate information (June 19, 2014) or last visit to an Intermountain Healthcare facility, whichever was greater. Kaplan-Meier curves are presented for the major adverse cardiovascular events outcomes.

Analyses examining an association between the primary outcome and CCTA identified levels of coronary artery plaque burden and CAC score, as well as subgroup analyses (including major baseline characteristics and calculated Framingham risk score), were similarly performed using Cox proportional hazards regression. Global *P* values for categorical explanatory variables were obtained using Cox proportional hazards regression. All *P* values were 2-sided, with a significance threshold of $P < .044$ for the primary outcomes and $P < .005$ for the secondary outcomes. Any variable with more than 20% missing data was not used in analysis. Any variable with 10% to 20% missing data was examined to determine the possibility of bias related to the missing data. For variables with less than 10% missing data, analyses were performed using only those patients with reported values, and no missing imputation methods were used. All analyses were conducted with SAS version 9.3 (SAS Institute Inc).

Safety Monitoring and Event Adjudication

Safety of the study was ensured by an independent data and safety monitoring board. Primary and secondary events were adjudicated by consensus of a 3-investigator team masked to study group and CCTA results.

Results

All 14 208 patients enrolled in the 45 clinics and practices of Intermountain Healthcare's Urban Central and North regions along the Wasatch Front of Northern Utah who were identified with diabetes in the Intermountain Healthcare electronic medical records were screened, and 4613 who qualified for inclusion by medical record review were approached for enrollment by research coordinators from Intermountain Medical Center, Salt Lake City, Utah. Of these, 3713 were excluded for reasons detailed in Figure 1. The remaining 900 patients from 45 clinics and practices provided informed consent, and 448 patients were randomized to the control group and 452 to the CCTA screening group.

Baseline Characteristics

Baseline characteristics of the study cohort, stratified by randomization group, are shown in **Table 1**. Randomization

Table 1. Baseline Characteristics for FACTOR-64 Randomization Groups

Baseline Characteristics	CCTA	
	No (n = 447)	Yes (n = 452)
Age, mean (SD), y	61.6 (8.35)	61.5 (7.94)
Men, No. (%)	235 (52.6)	234 (51.8)
Race/ethnicity, No. (%)		
White non-Hispanic	427 (95.5)	434 (96.0)
Hispanic	13 (2.9)	10 (2.2)
African American	1 (0.2)	2 (0.4)
Asian	3 (0.7)	2 (0.4)
American Indian	1 (0.2)	3 (0.7)
Native Hawaiian or other Pacific Islander	2 (0.4)	1 (0.2)
Body mass index, mean (SD)[a]	33.4 (7.05)	32.9 (6.76)
Former or current smoking, No. (%)	68 (15.4)	75 (16.6)
Diabetes mellitus		
Duration, mean (SD), y	13.5 (10.72)	12.3 (9.23)
Type, No. (%)		
1	52 (11.6)	56 (12.4)
2	395 (88.4)	396 (87.6)
Medications, No. (%)		
Noninsulin agent only	255 (57.1)	257 (57.0)
Insulin only	95 (21.2)	84 (18.6)
Both noninsulin agent and insulin	97 (21.7)	110 (24.4)
HbA_{1c}		
Mean (SD), %	7.5 (1.41)	7.4 (1.40)
Categories, No. (%)		
≤6.5	101 (23.4)	120 (28.0)
6.6-8.0	225 (52.2)	210 (49.1)
>8.0	105 (24.4)	98 (22.9)
Family history, No. (%)		
Diabetes mellitus	59 (13.2)	44 (9.7)
Cardiovascular disease	88 (19.7)	69 (15.3)
Comorbidities, No. (%)		
Hypertension	308 (68.9)	287 (63.5)
Hyperlipidemia	282 (63.1)	285 (63.1)
Hypothyroidism/hyperthyroidism	104 (23.3)	104 (23.0)
Depression	58 (13.0)	59 (13.1)
Gastroesophageal reflux disease	98 (21.9)	92 (20.4)
Sleep apnea	115 (25.7)	121 (26.8)
Asthma	48 (10.7)	45 (10.0)
Arthritis	11 (2.5)	8 (1.8)
Renal disease	32 (7.2)	33 (7.3)
Blood pressure, mean (SD), mm Hg		
Systolic	130.5 (11.49)	129.1 (12.45)
Diastolic	74.1 (7.71)	74.2 (8.41)
Statin use, No. (%)	322 (72.0)	346 (76.5)
Fasting lipid panel, mg/dL		
LDL-C, mean (SD)	87.7 (32.92)	86.3 (29.12)
HDL-C, mean (SD)	45.3 (13.41)	45.4 (14.04)
Triglycerides, median (IQR)	132 (92-198)	144 (99-201)
LDL-C categories, No. (%)[b]		
≤70	124 (30.3)	123 (30.2)
71-100	179 (43.8)	169 (41.4)
>100	106 (25.9)	116 (28.4)
Aspirin use, No. (%)	181 (40.5)	193 (42.7)
Creatinine, median (IQR), mg/dL	0.92 (0.80-1.10)	0.91 (0.79-1.10)

Abbreviations: CCTA, coronary computed tomography angiography; HbA_{1c}, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range.

SI conversion factors: To convert HDL-C and LDL-C values to mmol/L, multiply by 0.0259; to convert triglyceride values to mmol/L, multiply by 0.0113; to convert creatinine values to μmol/L, multiply by 88.4.

[a] Calculated as weight in kilograms divided by height in meters squared.

[b] Because of missing data, based on sample size of 409 and 408 for no CCTA and CCTA groups, respectively.

resulted in well-matched groups. The mean age was 62 years; the study population was approximately equally divided between men and women. Enrolled patients had a diagnosis of diabetes for an average of more than 12 years and had well-managed care, with baseline blood pressures, HbA_{1C} levels, and lipid measurements close to or exceeding Intermountain targets.

CCTA Screening Results and Treatment Recommendations

Of the 452 participants randomized to CCTA screening, 395 (87.4%) actually received a CT scan. Of women, 85.1% received CCTA and 14.9% received only CAC scoring, mainly because of an inability to adequately reduce heart rate (**Table 2**). Results of CCTA demonstrated a range of CAD, from none/minimal (31%) to mild (46%), moderate (12%), and severe (11%). A similar diversity was shown by CAC score, from none/minimal (36%) to mild (24%) to moderate-severe (41%). These results resulted in a recommendation for additional diagnostics, more aggressive risk factor reduction, or both, in more than two-thirds of patients (Table 2).

Primary and Secondary Clinical Outcomes

Results of both the primary and secondary clinical end points based on intention-to-treat as well as as-treated analyses during a mean follow-up to first primary event of 4.0 (SD, 1.7) years (CCTA group: median follow-up, 3.9 [range, 0.2-7.1] years; no CCTA group: median follow-up, 3.9 [range, 0.03-7.1] years) are shown in **Table 3**, **Figure 2**, and eFigure 2 in Supplement 2. Despite the longer than initially planned follow-up time, the primary end point event rate in the control group was less than half of expected. In the intention-to-treat analysis, the primary end point occurred in 6.2% of CCTA screened vs 7.6% of control group patients (HR, 0.80 [95% CI, 0.49-1.32]; P = .38). In the as-treated analysis, the respective event rates were 5.6% vs 7.9% (HR, 0.69 [95% CI, 0.41-1.16]; P = .16). No prespecified clinical end points, except a nominally significant result for heart failure hospitalization, differed between treatment groups in either analysis. Only 2 patients, 1 from each group, experienced worsening renal function by 30 days; however, in both, renal function returned to baseline by 1 year.

Diagnostic and Therapeutic Procedures

Follow-up procedures in the 2 groups, by intention-to-treat assignment and stratified by protocol-related vs symptom-driven indications, are shown in **Table 4**. Overall, randomization to CCTA resulted in 61 (14%) and 36 (8%) protocol-recommended coronary stress or noninvasive imaging tests and diagnostic coronary angiographic procedures, respectively, which resulted in 26 (5.8%) coronary revascularization procedures, including 7 CABG surgery procedures for multivessel CAD. Subsequent symptom-driven stress testing tended to be more common in the control group, whereas symptom-driven rates of diagnostic coronary angiography, percutaneous coronary intervention, and CABG surgery were similar. As-treated analyses showed similar results.

Table 2. Results of the Coronary CT Scans for the CCTA Group

	Measure
Total CT scans, No. (%)	395 (87.4)
Unable or unwilling to schedule scan, No. (%)	57 (12.6)
Days from enrollment to scan, mean (SD)	28.21 (37.19)
Days from enrollment to scan, median (IQR)	18 (13, 30)
CT type, No. (%)	
CAC only	59 (14.9)
CT, no CAC	2 (0.5)
CT and CAC	334 (84.6)
Reason for CAC only, No. (%)	
Heart rate >60/min	56 (94.9)
Creatinine	
≥2 mg/dL (men)	0
≥1.8 mg/dL (women)	1 (1.7)
Patient decision	1 (1.7)
Allergy	1 (1.7)
CAC score	
Median (IQR)	55 (0-332)
Category, No. (%)	
0-10, none/minimal	140 (35.6)
11-100, mild	93 (23.7)
>100, moderate-severe	160 (40.7)
Highest degree of stenosis, No. (%)	
Normal	105 (31.3)
Mild	155 (46.1)
Moderate	40 (11.9)
Severe	36 (10.7)
Highest degree of stenosis in a proximal vessel, No. (%)	
Normal	128 (38.1)
Mild	151 (44.9)
Moderate	36 (10.7)
Severe	21 (6.3)
Vessels with severe proximal disease, No. (%)	
0	315 (93.8)
1	18 (4.6)
2	2 (0.5)
3	1 (0.3)
LVEF	
Median (IQR), %	67 (62-72)
<40%, No. (%)	1 (0.31)
Medical treatment recommendation post CCTA, No. (%)	
Standard	118 (29.9)
Aggressive	277 (70.1)

Abbreviations: ; CAC, coronary artery calcium; CCTA, coronary computed tomography angiography; CT, computed tomography; IQR, interquartile range; LVEF, left ventricular ejection fraction.

SI conversion factor: To convert creatinine values to μmol/L, multiply by 88.4.

Exploratory Analysis of Changes in Risk Factors

Changes in critical quality indicators for diabetes medical management from baseline to 1 year for patients for whom data were available are shown in **Table 5.** Significant interval improvements were observed in all 3 lipid subfractions (LDL-C, HDL-C, triglycerides) in patients in the CCTA group,

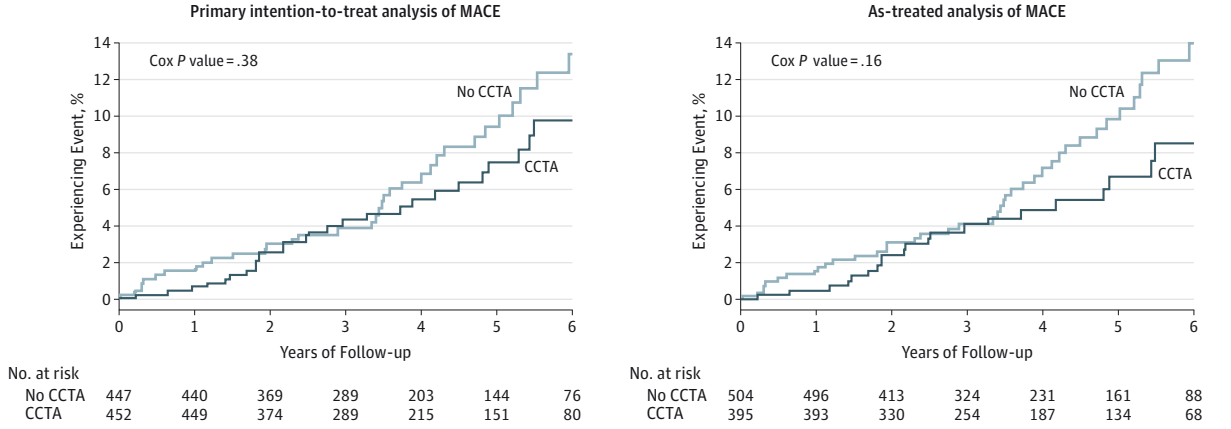
Table 3. Primary and Secondary Clinical End Points (Time to First Outcome)

Outcomes, No. (%)	Analysis							
	Intention to Treat				As Treated			
	CCTA				CCTA			
	No (n = 447)	Yes (n = 452)	HR (95% CI)	P Value[a]	No (n = 504)	Yes (n = 395)	HR (95% CI)	P Value[a]
Primary end point: death, nonfatal MI, or hospitalization for unstable angina	34 (7.6)	28 (6.2)	0.80 (0.49-1.32)	.38	40 (7.9)	22 (5.6)	0.69 (0.41-1.16)	.16
Death, all cause	19 (4.3)	16 (3.5)	0.82 (0.42-1.60)	.56	24 (4.8)	11 (2.8)	0.58 (0.28-1.18)	.13
Nonfatal MI	8 (1.8)	7 (1.5)	0.83 (0.30-2.28)	.72	8 (1.6)	7 (1.8)	1.05 (0.38-2.89)	.93
Hospitalization for unstable angina	9 (2.0)	9 (2.0)	0.94 (0.37-2.38)	.90	10 (2.0)	8 (2.0)	0.96 (0.38-2.43)	.93
MACE								
CV (CV death, nonfatal MI, or hospitalization for unstable angina)	23 (5.1)	21 (4.6)	0.89 (0.49-1.61)	.70	28 (5.6)	16 (4.1)	0.72 (0.39-1.33)	.30
CV death	8 (1.8)	7 (1.5)	0.86 (0.31-2.36)	.76	12 (2.4)	3 (0.8)	0.32 (0.09-1.12)	.07
Ischemic (CAD death, nonfatal MI, or hospitalization for unstable angina)	17 (3.8)	20 (4.4)	1.15 (0.60-2.19)	.68	22 (4.4)	15 (3.8)	0.86 (0.45-1.66)	.65
CAD death	2 (0.4)	5 (1.1)	2.45 (0.47-12.60)	.29	6 (1.2)	1 (0.3)	0.21 (0.03-1.76)	.15
Hospitalization for heart failure	10 (2.2)	3 (0.7)	0.26 (0.07-0.94)	.04	10 (2.0)	3 (0.8)	0.33 (0.09-1.20)	.09
Stroke or carotid revascularization procedure	9 (2.0)	8 (1.8)	0.85 (0.33-2.20)	.73	10 (2.0)	7 (1.8)	0.84 (0.32-2.20)	.71
Limb amputation or peripheral vascular revascularization procedure	0	2 (0.4)			0	2 (0.5)		

Abbreviations: CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular event; MI, myocardial infarction.

[a] Based on Cox proportional hazards regression.

Figure 2. Kaplan-Meier Event Survival Curves for the Primary Composite End Point of Major Adverse Cardiovascular Events (MACE; Death, Nonfatal Myocardial Infarction, or Hospitalization for Unstable Angina)



CCTA indicates coronary computed tomography angiography.

whereas no changes occurred in patients in the control group. Similarly, a favorable differential response was noted in blood pressure only in the intervention group. However, comparisons of changes between the 2 groups achieved significance only for HDL-C. In contrast, HbA_{1c} showed no change in either group. Consistent with the differential lipid changes, statin use at 1 year was greater in the CCTA group than in the control group (83.1 vs 75.7%, P = .008), as was high-intensity statin use (24.7 vs 19.7%, P = .02). The change in statin use was 3.7% for the no CCTA group and 6.6% for the CCTA group (P = .05), and the change in high-intensity statin use was 0.08% for the no CCTA group and 2.0% for the CCTA group (P = .13).

To determine whether responses within the intervention group differed by post-CCTA treatment recommendation, results at 1 year were stratified by assignment to standard or ag-

gressive medical therapy (**Table 6**). Significant improvements in both blood pressure and lipid panel targets were achieved among those recommended for aggressive risk factor reduction, whereas no interval changes occurred with assignment to standard therapy. However, comparisons of changes between the 2 groups achieved significance only for triglycerides. In contrast, no interval effect was found for HbA_{1C} in either treatment recommendation group. However, despite improvements noted for certain treatment targets in the CCTA group, overall success rates for reaching specified aggressive risk factor reduction care targets at 1 year among the 277 qualifying CCTA patients were generally below 50% (eTable 1 in Supplement 2).

Other Exploratory and Post Hoc Analyses

In post hoc analysis, the primary outcome was associated with and proportional to CAD burden assessed by both CCTA (mild CAD vs normal: HR, 3.96 [95% CI, 0.87-18.09]; P = .08; moderate/severe vs normal: HR, 5.38 [95% CI, 1.04-27.73]; P = .04) and by CAC scan (Agatston score 11-100 vs 1-10: HR, 2.00 [95% CI, 0.33-11.95]; P = .45; >100 vs 1-10: HR, 6.50 [95% CI, 1.50-28.20]; P = .01). The overall global P values were 0.12 for CCTA and 0.01 for CAC score. Subgroup analysis based on baseline characteristics and calculated Framingham risk score revealed no significant associations between these variables and the primary outcome (eTable 2 and eFigure 3in Supplement 2).

Discussion

The FACTOR-64 randomized trial evaluated whether routine CCTA screening of asymptomatic patients with diabetes (average disease duration >12 years) could beneficially influence clinical outcomes and risk factor control. Overall, annual event rates in both control and intervention groups were low (<2%), and outcomes (death, MI, or unstable angina) did not differ significantly between the CCTA and no CCTA groups after a mean of 4 years of follow-up.

Coronary computed tomography angiography involves significant expense and radiation exposure, so that justification of routine screening requires demonstration of net benefit in an appropriately high-risk population. We tested whether patients with long-standing diabetes represent such a group. Although CCTA screening demonstrated a marked diversity of CAD burden that was related to cardiovascular risk and led to more aggressive treatment recommendations for lipids, blood pressure, and glucose control in 70% of patients, which resulted in significant improvements in statin use and intensity, lipid fractions, and blood pressure levels, there was no advantage in reducing death and coronary heart disease outcomes. With the restrictions the protocol placed on contrast use according to baseline serum creatinine levels,

Table 4. Follow-up Procedures by Intention-to-Treat, Stratified by Protocol-Related vs Symptom-Driven Indications

Procedure	No. (%)	
	No CCTA (n = 447)	CCTA (n = 452)
Coronary stress or noninvasive imaging testing		
Protocol-related	NA	61 (13.5)
Symptom-driven	89 (19.9)	72 (15.9)
Total	89 (19.9)	133 (29.4)
Diagnostic coronary angiography		
Protocol-related	NA	36 (8.0)
Symptom-driven	23 (5.1)	24 (5.3)
Total	23 (5.1)	60 (13.3)
Percutaneous coronary intervention		
Protocol-related	NA	19 (4.2)
Symptom-driven	8 (1.8)	8 (1.8)
Total	8 (1.8)	27 (6.0)
Coronary artery bypass graft surgery		
Protocol-related	NA	7 (1.5)
Symptom-driven	6 (1.3)	6 (1.3)
Total	6 (1.3)	13 (2.9)

Abbreviations: CCTA, coronary computed tomography angiography; NA, not applicable.

Table 5. Changes in Critical Quality Indicators for Diabetes Medical Management From Baseline to 1 Year

Indicator	No CCTA			CCTA			P Value, No CCTA vs CCTA
	Sample Size[a]	Mean Difference (95% CI)	P Value[b]	Sample Size[a]	Mean Difference (95% CI)	P Value[b]	
HbA_{1c}, %	386	0.06 (−0.06 to 0.18)	.32	389	0.06 (−0.06 to 0.18)	.36	.53
Blood pressure, mm Hg							
Systolic	418	0.81 (−0.73 to 2.36)	.30	431	−1.34 (−2.98 to 0.29)	.11	.22
Diastolic	418	0.33 (−0.73 to 1.38)	.54	431	−1.28 (−2.25 to −0.31)	.01	.15
Fasting lipid panel, mg/dL							
LDL-C	374	−0.50 (−2.39 to 1.39)	.60	372	−2.64 (−4.69 to −0.59)	.01	.02
HDL-C	368	0.35 (−0.48 to 1.17)	.41	364	1.13 (0.33 to 1.93)	.006	.03
Triglycerides	375	−0.39 (−9.15 to 8.36)	.93	375	−5.54 (−11.38 to 0.29)	.06	.21

Abbreviations: HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

SI conversion factors: To convert HDL-C and LDL-C values to mmol/L, multiply by 0.0259; to convert triglyceride values to mmol/L, multiply by 0.0113.

[a] Based on analysis of patients for whom data were available.

[b] P values for pairwise intragroup comparisons obtained using paired t test and for intergroup comparisons using nonparametric tests of the differences.

Table 6. Changes in Critical Quality Indicators for Diabetes Medical Management From Baseline to 1 Year by Post-CCTA Treatment Recommendation

Indicator	Standard[a]			Aggressive[a]			*P* Value, Standard vs Aggressive
	Sample Size[b]	Mean Difference (95% CI)	*P* Value	Sample Size[b]	Mean Difference (95% CI)	*P* Value	
HbA_{1c}, %	100	0.02 (−0.20 to 0.23)	.88	247	0.04 (−0.11 to 0.19)	.62	.14
Blood pressure, mm Hg							
Systolic	110	−0.73 (−4.98 to 3.51)	.73	269	−1.74 (−3.56 to 0.09)	.06	.42
Diastolic	110	0.12 (−1.76 to 2.00)	.90	269	−1.94 (−3.19 to −0.69)	.003	.26
Fasting lipid panel, mg/dL							
LDL-C	93	−1.26 (−5.08 to 2.56)	.51	233	−4.06 (−6.70 to −1.42)	.003	.66
HDL-C	90	−0.33 (−1.77 to 1.71)	.97	229	1.32 (0.32 to 2.32)	.01	.14
Triglycerides	93	1.40 (−3.636.42)	.58	236	−7.68 (−14.58 to −0.78)	.03	.01

Abbreviations: CCTA, coronary computed tomography angiography; HbA_{1c}, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

SI conversion factors: To convert HDL-C and LDL-C values to mmol/L, multiply by 0.0259; to convert triglyceride values to mmol/L, multiply by 0.0113.

[a] Standard therapy targets: HbA_{1c} level less than 7.0%, low-density lipoprotein cholesterol level less than 100 mg/dL, systolic blood pressure less than 130 mm Hg. Aggressive therapy targets: HbA_{1c} level less than 6.0%, low-density lipoprotein cholesterol level less than 70 mg/dL, high-density lipoprotein cholesterol level greater than 50 mg/dL (women) or greater than 40 mg/dL (men), triglyceride level less than 150 mg/dL, systolic blood pressure less than 120 mm Hg.

[b] Based on analysis of patients for whom data were available.

no long-term adverse effects on renal function were observed in patients who received CCTA.

In a previous study, the DIAD (Detection of Ischemia in Asymptomatic Diabetics) Investigators[10] randomized 1123 asymptomatic patients with type 2 diabetes to undergo adenosine-stress myocardial perfusion imaging or no screening. Similar to our study, these authors noted a low cardiac event rate (2.9% in 4.8 years) and found no difference in the primary end point of cardiac death or nonfatal MI (HR, 0.88; *P* = .73). However, as with our study, evidence of CAD in the screened group predicted higher event rates. Unlike our study, DIAD was not designed as a treatment trial and did not provide a specific treatment plan based on myocardial perfusion imaging results.

There are several possible explanations for our results. First, despite specifically targeting enrollment of high-risk patients with diabetes (based on age and diabetes duration), the annual event rate was one-fourth of predicted, so the patients in this study were not actually at high risk. At study planning in 2006, a higher anticipated event rate was justified by our internal analysis within Intermountain Healthcare and further supported by published registries.[18] We attribute the lower event rate we observed within the FACTOR-64 study to the excellent medical management received by all enrollees, with baseline levels near or exceeding system targets for HbA_{1c}, LDL-C, and systolic blood pressure (Table 1). This high-quality care may be ascribed to the initiation in 1997 of the Intermountain Healthcare Diabetes Prevention and Management Development Team, which was charged with providing system-wide standards and therapeutic guidance and was fully functioning by 2005, thus making the differences in medical management between FACTOR-64 patients randomized to CCTA screening vs control less than might otherwise be expected.

Second, any effect of coronary revascularization for severe CAD on outcomes was limited by its much lower than anticipated incremental rate of application (5.8%). On the other hand, the benefit of revascularization applied as in FACTOR-64 may not be clinically relevant. Although our recommendations regarding coronary revascularization were similar to recently published national guidelines for improving survival in patients with severe CAD,[19] results from the BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes)[14] and COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation)[20] studies raise the question of whether revascularization can provide important incremental benefit over optimal medical therapy alone.

Strengths of our study include the relatively large size, the randomized study design, and the 4-year follow-up. Also, CCTA results were used to inform medical and procedural management using a standardized algorithm. The major limitation of our study was the unexpected low overall incidence of adverse events, limiting power to exclude a clinically important difference between the 2 study groups. This limitation arises from at least 3 sources: (1) the lower than expected annual event rates, (2) the overly optimistic assessment of risk reduction, and (3) the variable implementation of treatment recommendations by the broad spectrum of clinicians caring for these patients. Other potential limitations include that the study was performed in a single health system, some patients were lost to telephone follow-up, some patients were randomized to receive CCTA scanning but ultimately did not undergo the procedure, and information on functional status and cost was not available.

Conclusions

Among asymptomatic patients with type 1 or type 2 diabetes, use of CCTA to screen for CAD did not reduce the composite rate of all-cause mortality, nonfatal MI, or unstable angina requiring hospitalization at 4 years. These findings do not support CCTA screening in this population.

ARTICLE INFORMATION

Author Contributions: Dr Knight had full access to all 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: Muhlestein, Lappé, Lima, May, Towner, Anderson.
Acquisition, analysis, or interpretation of data: Muhlestein, Lappé, Lima, Rosen, May, Knight, Bluemke, Le, Bair, Vavare, Anderson.
Drafting of the manuscript: Muhlestein, Lappé, Lima, Knight, Anderson.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: May, Knight.
Obtained funding: Muhlestein, Lappé, Anderson.
Administrative, technical, or material support: Muhlestein, Lappé, Lima, Bluemke, Anderson.
Study supervision: Muhlestein, Lappé, Lima, Anderson.
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REFERENCES

1. Go AS, Mozaffarian D, Roger VL, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. *Circulation*. 2014;129(3):e28-e292.

2. Bax JJ, Young LH, Frye RL, Bonow RO, Steinberg HO, Barrett EJ; ADA. Screening for coronary artery disease in patients with diabetes. *Diabetes Care*. 2007;30(10):2729-2736.

3. Diabetes mellitus: a major risk factor for cardiovascular disease: a joint editorial statement by the American Diabetes Association; the National Heart, Lung, and Blood Institute; the Juvenile Diabetes Foundation International; the National Institute of Diabetes and Digestive and Kidney Diseases; and the American Heart Association. *Circulation*. 1999;100(10):1132-1133.

4. Giri S, Shaw LJ, Murthy DR, et al. Impact of diabetes on the risk stratification using stress single-photon emission computed tomography myocardial perfusion imaging in patients with symptoms suggestive of coronary artery disease. *Circulation*. 2002;105(1):32-40.

5. Grundy SM, Benjamin IJ, Burke GL, et al. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation*. 1999;100(10):1134-1146.

6. Tsujimoto T, Kajio H, Takahashi Y, et al. Asymptomatic coronary heart disease in patients with type 2 diabetes with vascular complications: a cross-sectional study. *BMJ Open*. 2011;1(2):e000139.

7. Wolk MJ, Bailey SR, Doherty JU, et al; American College of Cardiology Foundation Appropriate Use Criteria Task Force. ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2014;63(4):380-406.

8. Mark DB, Berman DS, Budoff MJ, et al; American College of Cardiology Foundation Task Force on Expert Consensus Documents. ACCF/ACR/AHA/NASCI/SAIP/SCAI/SCCT 2010 expert consensus document on coronary computed tomographic angiography: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. *J Am Coll Cardiol*. 2010;55(23):2663-2699.

9. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med*. 2008;359(22):2324-2336.

10. Young LH, Wackers FJ, Chyun DA, et al; DIAD Investigators. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. *JAMA*. 2009;301(15):1547-1555.

11. Rajagopalan N, Miller TD, Hodge DO, Frye RL, Gibbons RJ. Identifying high-risk asymptomatic diabetic patients who are candidates for screening stress single-photon emission computed tomography imaging. *J Am Coll Cardiol*. 2005;45(1):43-49.

12. Faglia E, Manuela M, Antonella Q, et al. Risk reduction of cardiac events by screening of unknown asymptomatic coronary artery disease in subjects with type 2 diabetes mellitus at high cardiovascular risk: an open-label randomized pilot study. *Am Heart J*. 2005;149(2):e1-e6.

13. Gibbons RJ. Asymptomatic patients with diabetes mellitus should not be screened for coronary artery disease. *J Nucl Cardiol*. 2006;13(5):616-620.

14. Frye RL, August P, Brooks MM, et al; BARI 2D Study Group. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med*. 2009;360(24):2503-2515.

15. Kwan AC, May HT, Cater G, et al. Coronary artery plaque volume and obesity in patients with diabetes: the factor-64 study. *Radiology*. 2014;272(3):690-699.

16. Gerstein HC, Miller ME, Byington RP, et al; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358(24):2545-2559.

17. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97(18):1837-1847.

18. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med*. 1998;339(4):229-234.

19. Fihn SD, Gardin JM, Abrams J, et al; American College of Cardiology Foundation; American Heart Association Task Force on Practice Guidelines; American College of Physicians; American Association for Thoracic Surgery; Preventive Cardiovascular Nurses Association; Society for Cardiovascular Angiography and Interventions; Society of Thoracic Surgeons. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2012;60(24):e44-e164.

20. Boden WE, O'Rourke RA, Teo KK, et al; COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med*. 2007;356(15):1503-1516.