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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Background

- Coronary artery disease (CAD) is a major cause of cardiovascular morbidity and mortality in patients with diabetes mellitus.
- Yet CAD is often asymptomatic, prior to myocardial infarction (MI) and death, potentially justifying routine screening.
- Prior attempts to assess screening for asymptomatic CAD have been limited to non-invasive tests that only detect myocardial ischemia, with variable sensitivity and specificity, and without a structured approach to therapy.

Coronary CT Angiography (CCTA)

- CCTA provides the opportunity to non-invasively evaluate both the extent and severity of coronary atherosclerosis.
- **FACTOR-64 Aim**: Assess whether routine screening for CAD by CCTA in higher risk patients with diabetes, and without signs or symptoms of cardiovascular disease, followed by CCTA-directed therapy, would reduce cardiovascular risk.

Study Description

- The FACTOR-64 study was a randomized clinical trial of 900 patients with type 1 or type 2 diabetes.
- Patients were recruited from 45 clinics and practices of a single health system (Intermountain Healthcare, Utah) and enrolled at a single-site coordinating center.
- Patients were randomized 1:1 to CAD screening with CCTA-directed therapy or to Intermountain Healthcare's systematized guidelines-directed optimal diabetes care.

Study Population

- Inclusion Criteria
  - Men: ≥50 years old with at least 3 years history of DM or ≥40 years old with at least 5 years history of DM
  - Women: ≥55 years old with at least 3 years history of DM or ≥45 years old with at least 5 years history of DM
  - Use of antidiabetic medication for at least 1 year
- Major Exclusions
  - Documented ASCVD (known CAD, history of MI, angina, CVA, TIA, cerebral or peripheral revascularization)
  - Limited life expectancy or pertinent co-morbidity
  - Unwilling or unable to provide consent

Diagnostic Testing in the CCTA Group

- Coronary arteriography and coronary artery calcium (CAC) scanning performed on a Toshiba Aquillon 64 CT scanner
  - Only a CAC score obtained if creatinine ≥2.0 mg/dl (men) or ≥1.8 mg/dL (women), contrast allergy or heart rate >60 bpm despite beta-blockade
- Scan results divided into 4 categories of severity
  - **Severe stenosis:** ≥70% in at least one proximal coronary artery
    - Recommended to undergo diagnostic coronary angiography
  - **Moderate stenosis:** Any 50% - 69% stenosis or CAC score >100
    - Recommended to undergo stress cardiac imaging followed by coronary angiography if clinically relevant myocardial ischemia detected
  - **Mild stenosis:** Any 10% - 49% stenosis or CAC score >10-100
  - **Normal:** <10% stenosis everywhere and CAC score ≤10

No further imaging studies recommended

Medical Management

- Standard optimal diabetes care
  - Recommended for all controls and CCTA patients with normal coronary artery scans
  - **Targets:** HgA1C<7.0%, LDL<100 mg/dL, systolic BP<130 mm Hg
- Aggressive risk factor reduction care
  - Recommended for all CCTA patients with at least some documented CAD
  - Emphasize diet and exercise
  - **Targets:** LDL<70 mg/dL, HDL>50 mg/dL, TG<150 mg/dL, HgA1C<6%, systolic BP<120 mm Hg

Enrollment and Follow-up

- Enrollment from July 9, 2007 to May 16, 2013
- Patients followed until August 1, 2014 (4.0±1.7 years)
- Endpoints
  - **Primary endpoint:** composite of all-cause mortality, non-fatal MI, and hospitalization for unstable angina
    - Estimated event rate was 8% per year; estimated effect size was 40%.
  - **Secondary endpoints:**
    - CV death alone and together with MI and unstable angina
    - CAD death alone and together with MI and unstable angina
    - Hospitalization for heart failure
    - Rise serum creatinine by ≥0.5 mg/dL at 30 days and persisting at one year
    - Stroke or carotid revascularization procedure
    - Change in HbA1c, blood pressure, lipids

Study Flow

Electronically screened: 14,208

Approached for enrollment: 4,613
- Letters with follow-up phone calls: 3,731
- Other methods for approach: 882

3,713 excluded
- 2,474 not on diabetic medications
- 1,233 met other exclusion criteria

(too short of diabetes diagnosis, other co-morbidities, unable to be contacted)
- 6 refused participation

900 Randomized

448 Randomized to be not scanned

452 Randomized to be scanned

1 withdrew immediately following randomization, excluded from further analyses

447 No CCTA Group*

452 CCTA Group*

***Primary Analysis**

Selected Baseline Characteristics

Baseline Characteristics	No CCTA (n = 447)	CCTA (n = 452)
Age, mean (SD), y	61.6 (8.35)	61.5 (7.94)
Male, No. (%)	235 (52.6)	234 (51.8)
Body Mass Index, mean (SD)	33.4 (7.05)	32.9 (6.76)
Smoking History or Current, No. (%)	68 (15.4)	75 (16.6)
DM duration , mean (SD), y	13.5 (10.72)	12.3 (9.23)
DM Type, No. (%)		
Type I	52 (11.6)	56 (12.4)
Type II	395 (88.4)	396 (87.6)
DM Medications, No. (%)		
Non-Insulin Agent Only	255 (57.1)	257 (57.0)
Insulin Only	95 (21.2)	84 (18.6)
Both Non-Insulin Agent and Insulin	97 (21.7)	110 (24.4)
Statin use, No. (%)	322 (72.0)	346 (76.5)
Aspirin use, No. (%)	181 (40.5)	193 (42.7)
Hemoglobin A1C, mean (SD), %	7.5 (1.41)	7.4 (1.40)
LDL Cholesterol, mean (SD), mg/dL	87.7 (32.9)	86.3 (29.1)

CCTA Results

Total CT scans: 395 (87.4%)

- CT type
  - CAC only = 59 (14.9%)
  - CT (no CAC) = 2 (0.5%)
  - CT and CAC = 334 (84.6%)
- Median CAC = 55 (IQR: 0, 332)
- CAC results by categories
  - 0-10 = 140 (35.6%)
  - 11-100 = 93 (23.7%)
  - >100 = 160 (40.7%)
- Highest degree of CCTA stenosis
  - Normal: 105 (31.3%)
  - Mild: 155 (46.1%)
  - Moderate: 40 (11.9%)
  - Severe: 36 (10.7%)
- Medical treatment recommendation post CCTA
  - Standard: 118 (29.9%)
  - Aggressive: 277 (70.1%)

Follow-up Procedures

		No CCTA	CCTA
Coronary stress/non-invasive imaging testing, No. (%)			
	Protocol	NA	61 (13.5)
	Symptom	89 (19.9)	72 (15.9)
	Total	89 (19.9)	133 (29.4)
Diagnostic coronary angiography, No. (%)			
	Protocol	NA	36 (8.0)
	Symptom	23 (5.1)	24 (5.3)
	Total	23 (5.1)	60 (13.3)
Percutaneous Coronary Intervention, No. (%)			
	Protocol	NA	19 (14.2)
	Symptom	8 (1.8)	8 (1.8)
	Total	8 (1.8)	27 (6.0)
Coronary artery bypass graft, No. (%)			
	Protocol	NA	7 (1.5)
	Symptom	6 (1.3)	6 (1.3)
	Total	6 (1.3)	13 (2.9)

Changes in Critical Quality Indicators for Diabetes Medical Management From Baseline to One Year

	ITT: Assignment to CCTA vs. no CCTA			Scanned Patients Assigned to Standard Versus Aggressive Medical Management		
	Sample Size (No CCTA, CCTA)*	**No CCTA mean difference (95% CI)**	**CCTA mean difference (95% CI)**	**Sample Size (Standard, Aggressive)***	**Standard mean difference (95% CI)**	**Aggressive mean difference (95% CI)**
HgA1c	(386, 389)	0.06 (-0.06, 0.18)	0.06 (-0.06, 0.18)	(100, 247)	0.02 (-0.20, 0.23)	0.04 (-0.11, 0.19)
BP, mmHg						
Systolic	(418, 431)	0.81 (-0.73, 2.36)	-1.34 (-2.98, 0.29)	(110, 269)	-0.73 (-4.98, 3.51)	-1.74 (-3.56, 0.09)
Diastolic	(418, 431)	0.33 (-0.73, 1.38)	-1.28 (-2.25, -0.31)	(110, 269)	0.12 (-1.76, 2.00)	-1.94 (-3.19, -0.69)
Lipid Panel (mg/dL)						
LDL	(374, 372)	-0.50 (-2.39, 1.39)	-2.64 (-4.69, -0.59)	(93, 233)	-1.26 (-5.08, 2.56)	-4.06 (-6.70, -1.42)
HDL	(368, 364)	0.35 (-0.48, 1.17)	1.13 (0.33, 1.93)	(90, 229)	-0.33 (-1.77, 1.71)	1.32 (0.32, 2.32)
TG	(375, 375)	-0.39 (-9.15, 8.36)	-5.54 (-11.38, 0.29)	(93, 236)	1.40 (-3.63, 6.42)	-7.68 (-14.58, -0.78)

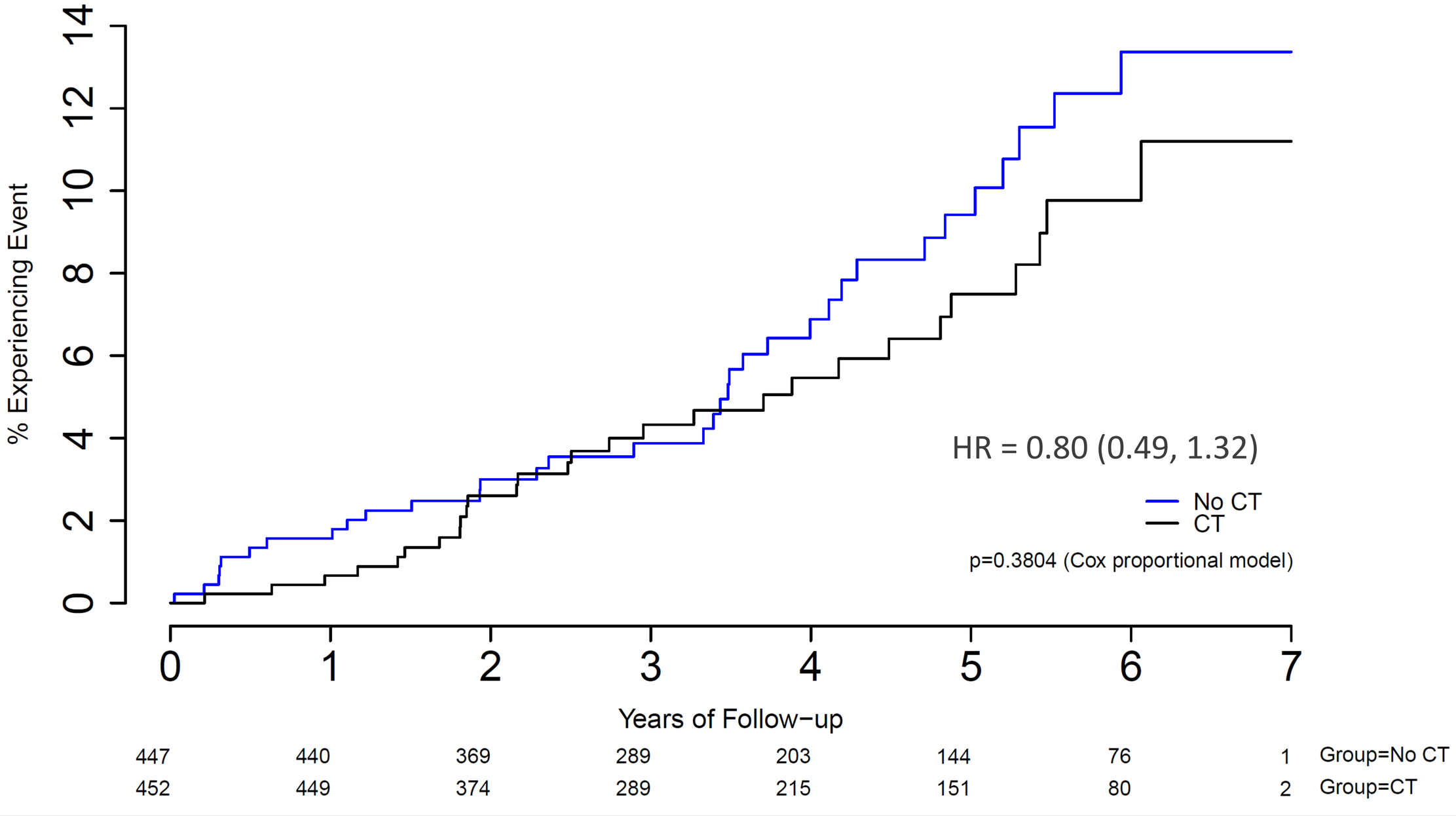
LDL = Low Density Lipoprotein, HDL = High Density Lipoprotein, TG = Triglycerides

*Based on analysis of patients for whom data were available.

Primary and Secondary Endpoints

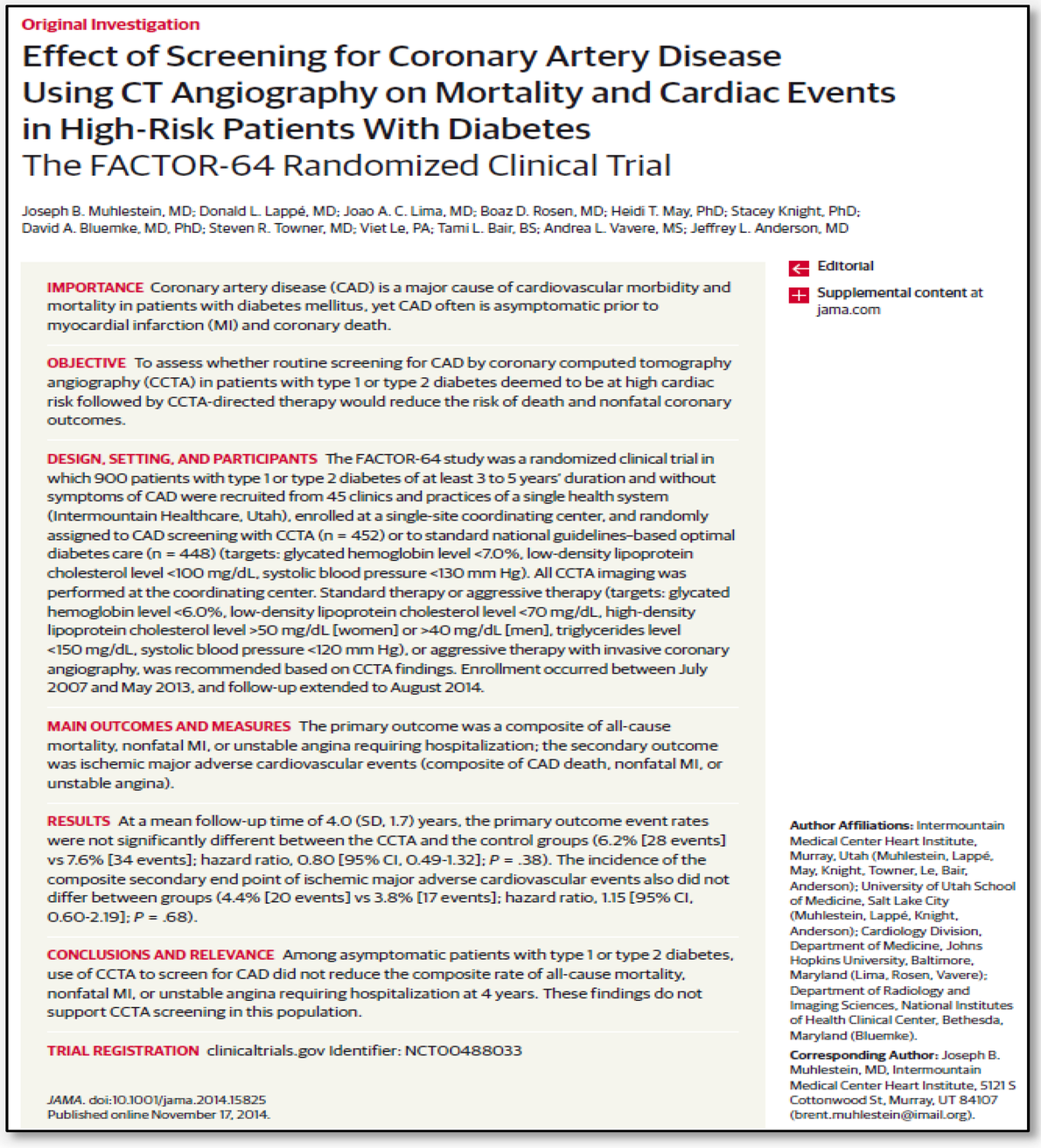
Outcomes, No. (%)	No CCTA (n=447)	CCTA (n=452)	Hazard Ratio (95% CI)	p-value
Primary endpoint: death/non-fatal MI, hosp. for USA	34 (7.6%) 1.9%/yr	28 (6.2%) 1.6%/yr	0.80 (0.49, 1.32)	0.38
Death (all cause)	19 (4.3)	16 (3.5)	0.82 (0.42, 1.60)	0.56
Non-fatal MI	8 (1.8)	7 (1.5)	0.83 (0.30, 2.28)	0.72
Hosp. for USA	9 (2.0)	9 (2.0)	0.94 (0.37, 2.38)	0.90
CV MACE: CV death/non-fatal MI/hosp. for USA	23 (5.1)	21 (4.6)	0.89 (0.49, 1.61)	0.70
CV death	8 (1.8)	7 (1.5)	0.86 (0.31, 2.36)	0.76
Ischemic MACE: CAD death/non-fatal MI, hosp. for USA	17 (3.8)	20 (4.4)	1.15 (0.60, 2.19)	0.68
CAD death	2 (0.4)	5 (1.1)	2.45 (0.47, 12.60)	0.29
Hosp. for HF	10 (2.2)	3 (0.7)	0.26 (0.07, 0.94)	0.04
Stroke/carotid revasc. procedure	9 (2.0)	8 (1.8)	0.85 (0.33, 2.20)	0.73

Primary Endpoint (Death/MI/Unstable Angina)



Conclusions

- Among asymptomatic patients with type 1 or type 2 diabetes, screening for CAD by CCTA did not reduce the composite rate of all-cause mortality, nonfatal MI, or hospitalization for unstable angina at 4 years despite differential use of coronary interventions and favorable trends in lipids and blood pressure.
- Overall, annual event rates in both control and intervention groups were low (<2%/yr).
  - This may be attributed to the excellent medical management received by all enrollees within Intermountain Healthcare, with baseline levels near or exceeding system targets for HgA1C, LDL-C, and systolic BP.
- These findings do not support CCTA screening in this population.



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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