Optimal Medical Therapy vs CT Angiography Screening for Patients With Diabetes
Raymond J. Gibbons, MD

Patients with diabetes mellitus have long been recognized as having a much greater incidence of coronary artery disease (CAD), which is a major factor in their poorer long-term outcomes. This has led to the recognition that patients with diabetes merit more intensive lipid treatment, which is reflected in the latest guidelines.

The true prevalence of CAD in asymptomatic patients with diabetes is unknown. Although retrospective studies of patients with diabetes undergoing stress testing have suggested a high prevalence that exceeds 50%, prospective analyses have shown significantly lower rates. A single population-based autopsy study suggested that the prevalence of anatomical CAD in persons with diabetes could be as high as 50% to 81%, depending on age and sex.

Because diabetes is associated with CAD and with a poorer outcome after the treatment of CAD with revascularization, early identification of CAD in patients with diabetes may be a reasonable approach to improve outcomes. Screening of asymptomatic patients for potentially life-threatening disease is intuitively attractive, an example of personalized medicine, and consistent with the widely quoted axiom “An ounce of prevention is worth a pound of cure.”

Successful screening for CAD requires a test that can provide prognostic information over and above traditional risk factors and can lead to a change in treatment that can improve outcomes compared with current practice. Cardiac imaging in asymptomatic patients with diabetes is theoretically capable of satisfying these criteria and therefore has been advocated by many.

The latest study of cardiac imaging in asymptomatic patients with diabetes is reported in in this issue of JAMA by Muhlestein et al. The authors used a population-based approach to screen 14,208 patients and ultimately enrolled 900 middle-aged asymptomatic patients with diabetes who were at risk for CAD and who met detailed inclusion and exclusion criteria. Patients were enrolled from 45 clinics and practices in a single health system (Intermountain Healthcare), and only 6 of the eligible patients reportedly refused participation. Patients were randomized to undergo CAD screening with coronary computed tomography angiography (CCTA) (n = 452) or to receive guidelines-based optimal diabetes care (n = 448). For patients randomized to CCTA, the investigators provided specific guidance to the patient’s clinician for coronary angiography and more aggressive risk factor modification. Revascularization was performed at the discretion of the clinician. The primary end point was the composite outcome of all-cause mortality, nonfatal myocardial infarction, and hospitalization for unstable angina.

At a mean follow-up of 4 years, the primary end point occurred in 6.2% of patients (28 events) in the CCTA group and in 7.6% patients (34 events) in the control group (HR, 0.80 [95% CI, 0.49-1.32]; P = .38). Follow-up was 99% complete. Abnormal findings on CCTA in the patients randomized to imaging was associated with subsequent cardiac events, consistent with previous literature.

The negative results of this trial will be disappointing to those who have advocated cardiac imaging for screening but are consistent with the prior negative results of the DIAD study, which randomly applied stress single-photon emission computed tomography (SPECT) myocardial perfusion imaging in asymptomatic patients with diabetes. The DIAD study was criticized for its failure to provide detailed advice to clinicians for management of therapy for patients with abnormal SPECT findings; that limitation was addressed in the design of the current study. The results reported by Muhlestein et al are also consistent with the results of the BARI-2D trial of revascularization in asymptomatic or mildly symptomatic patients with diabetes. Approximately one-sixth of the patients with diabetes enrolled in that trial were asymptomatic. Randomization to preferred revascularization with percutaneous coronary intervention or coronary artery bypass graft surgery did not improve outcomes.

There are several possible explanations for the failure of this well-conducted randomized trial to achieve its primary outcome. The first is that the assumption regarding the effect of CCTA may have been overly optimistic. Muhlestein et al assumed that CCTA would lead to additional risk factor modification, revascularization, or both in enough patients to reduce subsequent cardiac events by 40%. Although optimistic, a considerable reduction in events would be required to justify the effort and resources required for imaging and additional treatment as part of a screening strategy.

The negative results also may reflect the inability to successfully implement the more aggressive therapy recommended for patients with abnormal CCTA findings (as suggested by Table 4 and eTable 1 in the article by Muhlestein et al). The changes in blood pressure and low-density lipoprotein cholesterol (LDL-C) values from baseline to 1 year among patients randomized to CCTA did not differ significantly from those changes among patients in the control group. The only parameter that did differ, high-density lipo-
protein cholesterol values, was unlikely to have a major effect on patient outcomes because the between-group difference was less than 1 mg/dL. Revascularization was performed in 26 more patients in the group randomized to CCTA, but the rate of increased revascularization was modest (5.8%), reflecting the low prevalence (10.7%) of severe (>70%) stenosis, and the even lower prevalence (6.3%) of severe proximal stenosis. This modest prevalence of severe CAD is similar to that in the prospective DIAD study.

As suggested by the authors, the most likely explanation for the negative findings in this study was the excellent baseline medical therapy in these patients. The mean baseline LDL-C level in the control group (87.7 mg/dL) was 21 mg/dL to 32 mg/dL lower than that reported in 2 major trials enrolling patients with diabetes, even though more than 30% of the patients in those trials had a history of major macrovascular events.9-10 The mean baseline systolic blood pressure in the control group (130.5 mm Hg) in the study by Muhlestein et al was 8 mm Hg to 14 mm Hg lower than in these same 2 trials. Among patients in the control group, 74.1% had an LDL-C level less than 100 mg/dL, compared with 59.5% in BARI-2D. The subsequent rate of major cardiac events in the control group does not meet the usual 2% annual threshold for high risk.11 Thus, this trial was underpowered because patients in the control group did much better than anticipated in the sample size calculation because of their excellent baseline medical therapy.

What are the take-home messages from this randomized trial? Although studies like this are often characterized as “negative,” there are several important messages. As suggested by the authors, future randomized trials of cardiac imaging in asymptomatic patients with diabetes should be larger and focused on an enriched study population at higher risk. Such a strategy would certainly enhance the chances of success. A more important and more currently applicable message is that guideline-directed medical therapy for hypertension and hyperlipidemia is effective in asymptomatic patients with diabetes and should be implemented more consistently. The data in this study suggest that Intermountain Healthcare has set a new published standard for what is achievable in patients with diabetes with respect to blood pressure control and lipid-lowering therapy and that, when therapy is applied this effectively, patients with diabetes are no longer at high risk for major cardiovascular events.

Until future studies provide evidence of better patient outcomes with an imaging strategy, these results suggest that an “ounce of prevention” with optimal guideline-directed medical therapy in asymptomatic patients with diabetes is more important than cardiac imaging. The challenge for clinicians is to more consistently deliver optimal medical therapy to all patients with diabetes. As practicing physicians realize, there are many obstacles in the current health care system to the achievement of this goal, but overcoming them is essential to prevent cardiac events in patients with diabetes.

ARTICLE INFORMATION

Author Affiliation: Division of Cardiovascular Medicine, Mayo Clinic, Rochester, Minnesota.

Corresponding Author: Raymond J. Gibbons, MD, Division of Cardiovascular Medicine, Mayo Clinic, 200 First St SW, Rochester, MN 55905-0001 (raymond.raymond@mayo.edu).

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REFERENCES


