

London SW3 6NP

United Kingdom

E-mail: roxysenior@cardiac-research.org

<http://dx.doi.org/10.1016/j.jcmg.2016.04.001>

Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Coronary CT Angiography in Asymptomatic Type 2 Diabetic Patients: First Do No Harm?



We read with great interest the article by Kang et al. (1) on the prognostic value of coronary computed tomography angiography (CTA) in asymptomatic type 2 diabetes mellitus. We have several concerns regarding this study. First, the overall event rate was low: 37 cardiac events in 29 patients (an overall event rate of 6.2%). The reported event-free survival rates must be interpreted in the context of the low event rates. Second, the use of medical therapy was low across the study population (<40% for all 3 subgroups). It is also unclear as to why 34.8% of asymptomatic patients with obstructive coronary artery disease (CAD) underwent revascularization. Was the decision to revascularize based on the oculocardiac reflex? Of the 10 cardiac deaths, how many of these occurred following revascularization? What is even more perplexing is that for the high-risk subgroup of patients with obstructive CAD, despite some of these patients undergoing revascularization, the use of medical therapy remained suboptimal (only 31.6% were on a lipid-lowering agent).

How would appropriate uptake of optimal medical therapy without screening coronary CTA alter the management and outcomes for this study population? Using the current American College of Cardiology/American Heart Association (ACC/AHA) atherosclerotic cardiovascular disease calculator (2),

a typical patient with normal coronary arteries in this study has a 5.6% 10-year risk of heart disease or stroke, with the ACC/AHA recommending moderate-intensity statin therapy; a typical patient with non-obstructive CAD in this study has a 19.4% 10-year risk of heart disease or stroke, with the ACC/AHA recommending high-intensity statin therapy and consideration of aspirin; a typical patient with obstructive CAD in this study has a 23.4% 10-year risk of heart disease or stroke, with the ACC/AHA recommending high-intensity statin therapy and consideration of aspirin (2). One can hypothesize that following current ACC/AHA guidelines, event rates in this study population would have been even lower with appropriate medical therapy alone, without screening coronary CTA. The FACTOR-64 (Screening For Asymptomatic Obstructive Coronary Artery Disease Among High-Risk Diabetic Patients Using CT Angiography, Following Core 64) study was a randomized study examining the role of screening coronary CTA in 900 asymptomatic patients with type 1 or type 2 diabetes mellitus (3). At a mean follow-up duration of 4.0 years, there were no significant differences in the primary composite endpoint of all-cause mortality, nonfatal myocardial infarction, or unstable angina requiring hospitalization between the coronary CTA and control groups (3). It should be emphasized that a high proportion of patients in both the coronary CTA and control groups of the FACTOR-64 study were on statin therapy (76.5% and 72%, respectively) (3). Further evidence against routine screening of diabetic patients for asymptomatic CAD comes from the DIAD (Detection of Ischemia in Asymptomatic Diabetics) study, a randomized controlled trial in which 1,123 patients were randomly assigned to either screening with adenosine stress myocardial perfusion imaging (MPI) or not (4). It was found that screening for asymptomatic CAD with MPI in diabetic patients did not significantly reduce the cardiac event rates (4). During the course of the DIAD study there was a significant increase in the use of statin therapy in both groups (from 41% to 67% for the control group and from 37% to 67% for the MPI group; $p < 0.05$) (4).

Most importantly, retrospective electrocardiogram (ECG) gating was used to perform coronary CTA for the current study. Retrospective ECG gating is associated with significantly higher radiation exposure and potential cancer risk compared with prospective ECG gating (5). The dose-length product and effective radiation dose for each coronary CTA examination were not reported. Given that 52.2% of the patients with normal coronary arteries in this study were middle-aged women, the potential significance of

radiation exposure in these asymptomatic patients cannot be understated. While coronary CTA provides detailed anatomic assessment of coronary atherosclerotic disease burden, a routine coronary CTA does not provide any functional information about the presence and extent of myocardial ischemia. Performing an investigation in any truly asymptomatic patient population is fraught with risks and potential ethical and clinical dilemmas in interpreting and dealing with the investigation results. When a good clinician orders an investigation, *primum non nocere* should always be the first guiding principle.

Bo Xu, MB BS (Hons)*

L. Leonardo Rodriguez, MD

Serge Harb, MD

Wael Jaber, MD

*Section of Cardiovascular Imaging

Heart and Vascular Institute

Cleveland Clinic

Desk J1-5

9500 Euclid Avenue

Cleveland, Ohio 44195

E-mail: xub@ccf.org

<http://dx.doi.org/10.1016/j.jcmg.2016.12.014>

Please note: The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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THE AUTHORS REPLY:



We thank Dr. Xu and colleagues for their comments on our paper (1).

Coronary artery disease (CAD) is the major cause of mortality in patients with type 2 diabetes. Consequently, there has been substantial interest in the early detection and treatment for asymptomatic CAD in these patients. Even in the DIAD (Detection of Ischemia in Asymptomatic Diabetics) study, patients

with moderate-to-large ischemia had a 6-fold greater cardiac risk than did those with normal or small perfusion defects. A post hoc analysis also showed that the incidence of cardiac events was higher in the high-risk group classified by the UKPDS (United Kingdom Prospective Diabetes Study) risk engine (1.2% in low risk vs. 2.5% in intermediate risk vs. 9.9% in high risk; $p = 0.002$). Compared with the DIAD and FACTOR-64 (Screening For Asymptomatic Obstructive Coronary Artery Disease Among High-Risk Diabetic Patients Using CT Angiography, Following Core 64) trials, our study showed relatively lower cardiac event rates. However, a more important finding was that there was a significant difference in cumulative cardiac event rates according to severity of CAD (0.6% in normal coronary arteries vs. 3.0% in nonobstructive CAD vs. 11.2% in obstructive CAD; $p < 0.001$). These findings suggest that we should focus on finding high-risk patients even in asymptomatic type 2 diabetes.

In the present study we enrolled study participants between February 2008 and June 2012. However, the levels of glucose, lipid, and blood pressure control in participants were comparable with those of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) and ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) trials. Accordingly, we think that our study participants represent contemporary patients with type 2 diabetes. In addition, to resolve an issue of medication use, please see **Figure 1**. On the other hand, the 2013 guidelines of the American College of Cardiology/American Heart Association for the management of cholesterol expanded the statin treatment to nearly all adult diabetic patients. We also agreed that clinical evaluation of asymptomatic diabetic patients after the application of the new guidelines is necessary.

In our study, to avoid the limitation of coronary computed tomography angiography (CTA), patients with obstructive CAD on coronary CTA were recommended to undergo invasive coronary angiography or stress test (exercise electrocardiography or myocardial perfusion imaging). Also, to avoid unnecessary revascularizations, we followed the management strategy of the BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) study, which included asymptomatic type 2 diabetic patients (17.9%), and revascularization was only performed in patients with CAD documented on angiography ($\geq 50\%$ stenosis of a major epicardial coronary artery associated with a positive stress test or $\geq 70\%$ stenosis of a major epicardial coronary artery). In addition, among 10 cardiac deaths, 4 had a prior history of coronary revascularization.