JACC: CARDIOVASCULAR IMAGING
VOL. 11, NO. 10, 2018
© 2018 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Paradigms of Noninvasive Assessment of Coronary Atherosclerosis in Diabetic Patients

Insights From the PARADIGM Registry*

Maros Ferencik, MD, PhD, MCR

The prevalence of diabetes mellitus has been increasing over the past 2 to 3 decades, with an estimated 23.4 million adults with diagnosed diabetes living in the United States in 2018 (1). Diabetes mellitus is a major cardiovascular risk factor, and patients with diabetes have an approximately 2-fold increased risk of all-cause death, vascular death, and coronary artery disease (2,3). Diabetic patients also have an increased prevalence of subclinical atherosclerosis, determined as the presence of coronary artery calcium, higher calcium scores, and faster progression of coronary calcium (4,5). However, in diabetic patients with no or low coronary artery calcium scores, cardiovascular event rates were very low, suggesting that diabetes cannot be used as coronary artery disease equivalent in all patients (6). The relationship between traditional cardiovascular risk factors and cardiovascular events was only partially explained by coronary calcium scores, suggesting that noncalcified plaque and/or other nonatherosclerotic factors were also significantly contributing to the increased risk of cardiovascular events (7).

Coronary computed tomography (CT) angiography is a reliable noninvasive technique for the evaluation of coronary plaque, including noncalcified plaque components, quantitative plaque measurements, and high-risk plaque detection (8–11). Serial assessment of coronary CT angiography allows us to evaluate changes in plaque volumes and monitor effects of medical therapies (12). The prognostic value of coronary artery calcium progression for future cardiovascular events is well established (13). There is also growing interest in imaging of noncalcified atherosclerotic plaque and high-risk plaque features for the prediction of future events (9,14). The specific plaque characteristics of coronary plaques and natural history of plaque progression in patients with diabetes mellitus have not been fully evaluated.

SEE PAGE 1461

In this issue of *iJACC*, Kim et al. (15) report the results of the detailed coronary plaque analysis in the PARADIGM (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography IMaging) registry. The authors specifically focused on the subgroup of patients with diabetes mellitus. The analyses included 1,602 patients, of whom 372 had a history of diabetes mellitus. To account for the baseline differences between diabetic and nondiabetic patients, the authors performed propensity matching in a subgroup of patients. All patients included in the study underwent 2 coronary CT angiography examinations over a period of at least 24 months. This approach permitted serial assessment of quantitative and qualitative coronary atherosclerotic plaque characteristics. The mean time between the first and second CT scan was almost 4 years. A few important observations from the presented analyses could be highlighted. In the entire cohort, plaque progression occurred more often in patients with diabetes. Diabetes mellitus, male sex, hypertension, and mean plaque burden ≥75% at baseline were associated with plaque progression, whereas treatment with statins was protective against plaque progression in multivariable analysis. Among patients

*Editorials published in *JACC: Cardiovascular Imaging* reflect the views of the authors and do not necessarily represent the views of *JACC: Cardiovascular Imaging* or the American College of Cardiology.

From the Knight Cardiovascular Institute, Oregon Health and Science University, Portland, Oregon; and the Cardiac MR PET CT Program, Department of Radiology, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts. Dr. Ferencik was supported by Fellow to Faculty Award 13FTF16450001 from the American Heart Association.

ISSN 1936-878X/$36.00
https://doi.org/10.1016/j.jcmg.2018.04.024

with diabetes, male sex and mean plaque burden ≥75% at baseline were associated with plaque progression. In the matched analysis, patients with diabetes displayed a greater percent change of total plaque volume and necrotic-core plaque volume (low CT attenuation plaque) during follow-up. In the qualitative analysis of high-risk plaque features, there was a trend toward an increase in low CT attenuation plaque and spotty calcium in patients with diabetes. Interestingly, patients with diabetes had lower low-density lipoprotein cholesterol at baseline and follow-up, but despite this, they showed more pronounced progression of atherosclerosis. Furthermore, the progression of plaque was associated with higher levels of hemoglobin A1c. There was no significant difference in the composite major adverse cardiovascular events of death, myocardial infarction, and revascularization between patients with and without diabetes.

The major strength of the paper is the inclusion of a large population of patients with detailed quantitative and qualitative coronary plaque analyses. The study underscores the ability of noninvasive plaque imaging by CT to provide important mechanistic insights into the characterization and natural history of coronary atherosclerosis. There are some limitations that the readers need to take into account when interpreting the results of the study. The population predominantly included patients from East Asia with fairly low body mass index (mean body mass index of ~25 kg/m^2 compared with ~28 to 30 kg/m^2 typically reported in North American and European studies). Despite favorable patient characteristics, almost 22% of patients were excluded from the analysis due to image quality insufficient for quantitative coronary CT angiography measurements. This percentage is higher than some previously reported exclusion rates, and highlights the need for excellent image quality if prospective studies using quantitative plaque assessment are considered (12,16).

The authors were unable to provide information on the original population of patients that was used to select the PARADIGM registry patients. Only patients who had 2 consecutive CT scans that were both clinically indicated were included in the study. This introduces an important selection bias, as only patients who had an indication for a follow-up CT scan were included. It can be assumed that this was a small minority of all patients who underwent the first coronary CT angiography. Therefore, the results of the study are applicable to this very specific population.

The authors followed the study participants for almost 4 years after the second CT scan and reported the occurrence of major cardiovascular events. The event rates for hard cardiovascular events (death or myocardial infarction) were very low. The majority of reported major cardiovascular events were revascularizations. The authors only reported numbers and percentages of events. They did not perform survival analysis, which would be more informative. We may speculate that the majority of revascularizations occurred shortly after the second CT scan and perhaps reflected the findings of obstructive coronary artery disease on coronary CT angiography. From that perspective, the selection of patients who underwent clinically indicated second CT scan biases toward imaging patients who had clinically significant progression of coronary artery disease.

A more detailed analysis of traditional assessment of coronary CT angiography for stenosis was not included in the paper. The authors reported the prevalence of significant stenosis at baseline, but stenosis was not included in the multivariable models assessing plaque progression. The progression of obstructive coronary artery disease between baseline and follow-up scan was not reported. We know from prior studies that the presence of significant stenosis is strongly associated with future cardiovascular events (9,11,17,18). The progression to obstructive disease is also an important factor for prediction of clinical cardiovascular events. In future studies, it will be important to evaluate plaque characteristics after adjusting for significant stenosis and to also study the natural history of the progression of obstructive coronary artery disease. The relationship among large plaque burden, high-risk plaques, and risk of future cardiovascular events has been observed in both intravascular imaging and coronary CT angiography studies (18,19). High-risk plaque characteristics play an important role in the rapid progression of coronary lesions to obstruction through cycles of plaque rupture and healing (14). Indeed, the PARADIGM study findings of higher plaque progression, predictive value of larger plaque burden for plaque progression, and increase of high-risk plaque prevalence and low CT attenuation plaque volume during follow-up in patients with diabetes provide a mechanistic explanation for the observed increased risk of cardiovascular events in other diabetic populations.

The authors demonstrated higher levels of hemoglobin A1c in subjects with plaque progression at follow-up CT scan. These findings suggest a potential role of tighter glucose control in preventing plaque progression, although the results from randomized trials showed only a modest effect of intensive glucose control on cardiovascular outcomes (20).

The levels of low-density lipoprotein cholesterol decreased from baseline to follow-up in patients with diabetes. However, the average level of low-density lipoprotein cholesterol in patients with diabetes was 87 mg/dl, not reaching the goal of <70 mg/dl. The observed higher progression of plaque and especially low CT attenuation plaque volumes in diabetic patients is a testament to the need for intense lipid lowering that can lead to slowing or even reversal of the progression of coronary atherosclerosis and also to a shift toward stable coronary lesions with increase in dense calcified plaque and decrease in low CT attenuation plaque (12,21,22).

In summary, the observations from the PARADIGM registry expand our knowledge of the natural history of coronary atherosclerosis as assessed by noninvasive coronary CT angiography, especially in the high-risk diabetic population. The results of the study provide information on the underpinnings of increased atherosclerotic risk in patients with diabetes mellitus and support future interventional studies focused on the improvement of outcomes. Data from the study by Kim et al. (15) may play an important role in planning interventional trials and provide support for the use of CT-derived plaque measures as potential surrogate endpoints.

ADDRESS FOR CORRESPONDENCE: Dr. Maros Ferencik, Knight Cardiovascular Institute, Oregon Health and Science University, 3180 Sam Jackson Park Road, Mail Code UHN62, Portland, Oregon 97239. E-mail: ferencik@ohsu.edu.

REFERENCES

1. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. Circulation 2018;137:e67–492.

2. Sarwar N, Gao P, Seshasai SR, et al., for the Emerging Risk Factors Collaboration. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 2010; 375:2215–22.

3. Rao Kondapally Seshasai S, Kaptoge S, Thompson A, et al. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011;364:829–41.

4. Bertoni AG, Kramer H, Watson K. Post WS diabetes and clinical and subclinical CVD. Glob Heart 2016;11:337–42.

5. Kronmal RA, McClelland RL, Detrano R, et al. Risk factors for the progression of coronary artery calcification in asymptomatic subjects: results from the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation 2007;115:2722–30.

6. Malik S, Budoff MJ, Katz R, et al. Impact of subclinical atherosclerosis on cardiovascular disease events in individuals with metabolic syndrome and diabetes: the Multi-Ethnic Study of Atherosclerosis. Diabetes Care 2011;34:2285–90.

7. Yeboah J, Delaney JA, Nance R, et al. Mediation of cardiovascular risk factor effects through subclinical vascular disease: the Multi-Ethnic Study of Atherosclerosis. Arterioscler Thromb Vasc Biol 2014;34:1778–83.

8. Achenbach S, Moselewski F, Ropers D, et al. Detection of calcified and noncalcified coronary atherosclerotic plaque by contrast-enhanced, submillimeter multidetector spiral computed tomography: a segment-based comparison with intravascular ultrasound. Circulation 2004;109:14–7.

9. Motoyama S, Ito H, Sarai M, et al. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid-term follow-up. J Am Coll Cardiol 2015;66:337–46.

10. Voros S, Rinehart S, Qian Z, et al. Coronary atherosclerosis imaging by coronary CT angiography: current status, correlation with intravascular interrogation and meta-analysis. J Am Coll Cardiol Img 2011;4:537–48.

11. Ferencik M, Mayrhofer T, Bittner DO, et al. Use of high-risk coronary atherosclerotic plaque detection for risk stratification of patients with stable chest pain: a secondary analysis of the PROMISE randomized clinical trial. JAMA Cardiol 2018;3:144–52.

12. Auscher S, Heinsen L, Nieman K, et al. Effects of intensive lipid-lowering therapy on coronary plaques composition in patients with acute myocardial infarction: assessment with serial coronary CT angiography. Atherosclerosis 2015;241: 579–87.

13. McEvoy JW, Blaha MJ, DeFilippis AP, et al. Coronary artery calcium progression: an important clinical measurement? A review of published reports. J Am Coll Cardiol 2010;56:1613–22.

14. Ahmadi A, Leipsic J, Blankstein R, et al. Do plaques rapidly progress prior to myocardial infarction? The interplay between plaque vulnerability and progression. Circ Res 2015;117:99–104.

15. Kim U, Leipsic JA, Sellers SL, et al. Natural history of diabetic coronary atherosclerosis by quantitative measurement of serial coronary computed tomographic angiography: results of the PARADIGM study. J Am Coll Cardiol Img 2018; 11:1461–71.

16. Ferencik M, Mayrhofer T, Puchner SB, et al. Computed tomography-based high-risk coronary plaque score to predict acute coronary syndrome among patients with acute chest pain—results from the ROMICAT II trial. J Cardiovasc Comput Tomogr 2015;9:538–45.

17. Chow BJW, Small G, Yam Y, et al. Incremental prognostic value of cardiac computed tomography in coronary artery disease using CONFIRM: COroNary computed tomography angiography evaluation for clinical outcomes: an InteRnational Multicenter registry. Circ Cardiovasc Imaging 2011; 4:463–72.

18. Tesche C, Plank F, De Cecco CN, et al. Prognostic implications of coronary CT angiography-derived quantitative markers for the prediction of major adverse cardiac events. J Cardiovasc Comput Tomogr 2016;10:458–65.

19. Stone GW, Maehara A, Lansky AJ, et al. A prospective natural-history study of coronary atherosclerosis. N Engl J Med 2011;364: 226–35.

20. Ray KK, Seshasai SRK, Wijesuriya S, et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. Lancet 2009;373: 1765–72.

21. Puri R, Nicholls SJ, Shao M, et al. Impact of statins on serial coronary calcification during atheroma progression and regression. J Am Coll Cardiol 2015;65:1273–82.

22. Räber L, Taniwaki M, Zaugg S, et al. Effect of high-intensity statin therapy on atherosclerosis in non-infarct-related coronary arteries (IBIS-4): a serial intravascular ultrasonography study. Eur Heart J 2015;36:490–500.

KEY WORDS computed tomography, coronary artery, diabetes mellitus, plaque, progression