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Non-invasive imaging in assessment of the asymptomatic diabetic patient: Is it of value?

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Type 2 diabetes is increasing in prevalence and is associated with at least a two-fold increased risk of cardiovascular mortality.[1] While diabetes has been widely considered a coronary heart disease (CHD) equivalent—implying a 10-year cardiovascular risk of >20% for every diabetes patient[2]—increasing data refute this assertion. A recent systematic review and meta-analysis of 13 studies involving 45,108 patients followed for a mean of 13.4 years showed that patients with diabetes without prior myocardial infarction had a 43% lower risk of developing total CHD events compared with patients without diabetes with previous myocardial infarction (summary odds ratio 0.56, 95% confidence interval 0.53-0.60).[3] New guidelines have begun to acknowledge the heterogeneity in risk and include different treatment recommendations for diabetic patients without other risk factors who are considered to be at lower risk.[4,5] Thus, to consider diabetes a coronary heart disease equivalent may no longer be warranted, raising the possibility that non-invasive testing might be useful in distinguishing levels of risk and guiding management in the asymptomatic diabetic patient.

In this issue of the Journal, van den Hoogen et al[6] report a study on the value of coronary CT angiography in diabetic patients without chest pain. This editorial point of view seeks to consider this manuscript in the context of a broader discussion of the value of non-invasive imaging in assessment of these patients.

CORONARY ARTERY CALCIUM (CAC) SCANNING

CAC is a direct marker of coronary artery atherosclerosis and has been shown to be a powerful predictor of risk, consistently providing risk stratification beyond global risk scores.[7-10] Multiple studies have addressed the prognostic value of CAC scanning in the asymptomatic diabetic patient. Raggi et al[11] reported findings in 10,377 asymptomatic individuals, of whom 903 were type 2 diabetes mellitus patients, followed up for an average of 5 years. For any degree of CAC abnormality, all-cause mortality was higher in diabetic vs non-diabetic patients. However, 39% of the diabetic

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patients had either a zero CAC score or low score <10), and in this group, the risk of death was only slightly higher than in non-diabetic patients at 5 years (~1%). Thus, short-term mortality risk appeared to be low among the more than one-third of diabetics with very low CAC scores.

The high prevalence of the absence of coronary calcification—CAC 0—in the asymptomatic diabetic patient has now been shown in two large population-based studies. In the Multi-Ethnic Study of Atherosclerosis (MESA), 38% of patients with diabetes had a CAC score of 0.[12] In the similar Heinz Nixdorf Recall (HNR) study, 39.3% of women with diabetes and 13.4% of men with diabetes had a CAC score of 0.[13] The MESA and HNR both also demonstrated that CAC provided incremental prognostic value over traditional risk factors in the asymptomatic diabetic patient. In a report combining data from the MESA and HNR studies,[14] CAC was a better predictor of incident cardiovascular events compared to the Framingham Risk Score and the United Kingdom Prospective Diabetes Study (UKPDS).

Potentially, the demonstration of a zero or low CAC score might be useful in modifying the potential intensity of medical management among diabetics. For instance, in an observational study of 2384 patients with diabetes, of whom 162 died after a follow-up of 5.6 + 3 years, Silverman et al[15] reported that CAC allowed the discrimination of patients at lower risk for whom aspirin preventive treatment might not be beneficial. Potentially, a low CAC score might be useful in developing a more ''wait and see'' attitude among patients who have statin intolerance. A low CAC score may also be useful in guiding the intensity of follow-up of visits and the threshold for downstream stress testing (higher threshold with low CAC scores) among diabetic patients.

CORONARY CT ANGIOGRAPHY

Coronary CTA has extended the potential applications of CT in the asymptomatic diabetic patient, by providing an accurate assessment of non-calcified coronary plaque and coronary stenosis. Despite the youth of the modality, the use of coronary CTA in asymptomatic patients with diabetes has already been reported in numerous studies.[16,17] The overall conclusion from these studies is that the findings from CTA are heterogeneous and include both (1) patients with diabetes who have a high prevalence of coronary atherosclerosis, obstructive CAD, and higher prevalence of adverse plaque features compared to non-diabetic subjects, while (2) a substantial proportion of these patients have entirely normal coronary CTA with no evidence of atherosclerotic plaque.

Prevalence of Coronary Atherosclerosis and Any Plaque on Coronary CTA

Coronary CTA allows the assessment of non-calcified plaque and coronary stenosis as well as calcified plaque. The proportion of patients having ≥50% stenosis on coronary CTA has generally ranged from 24% to 32%. Eight prior studies reported both CAC (including the CAC 0) categories and coronary plaque as seen on coronary CTA in asymptomatic diabetic.[16-23] Of 1747 patients in these studies, 38% (659 patients) had CAC 0—an identical percentage to that seen in the MESA study. On coronary CTA, 26% (455 patients) had entirely normal studies—i.e., no non-calcified or calcified plaque. In a recent study, Park et al compared coronary CTA findings in 1017 self-referred asymptomatic diabetic individuals (age 56 ± 8 years) to 1017 non-diabetic subjects propensity matched for 19 baseline clinical variables.[24] While any plaque on CCTA was more prevalent in those with diabetes than in those without [58.4% vs 51.29%, respectively ($P = 0.001$)], 41.6% of the diabetic subjects had no coronary plaque. The lower prevalence of coronary plaque in these individuals compared to those in the other reported studies is likely due to their being subjects who referred themselves for coronary CTA, rather than patients referred clinically for the examination.[25]

Prediction of Cardiac Events

As within other patient groups, coronary CTA has been shown to have strong prognostic value in asymptomatic diabetic patients. Park et al followed 557 asymptomatic diabetic Korean patients after coronary CTA for cardiac events, including cardiac death, non-fatal MI, acute coronary syndromes, and late revascularization.[17] Atherosclerosis was observed in 71% of the patients, of whom 31% had significant (>50%) stenosis, and 17% had significant stenosis in the LM or proximal LAD. During a mean follow-up of 34 months, the prognosis was excellent for patients without atherosclerosis (0.5% total event rate). The patients with atherosclerosis but no stenosis had worse outcomes than those without coronary atherosclerosis. The event rate was further elevated in those with significant stenosis by CT (7.1%) and stenosis of the left main or proximal LAD (10.9%). Min et al provided the first study to examine the ability of coronary CTA to improve risk stratification over the CAC score. They reported findings from the multinational CONFIRM registry in 400 asymptomatic patients with diabetes who underwent coronary CTA as well as CAC scanning and were followed for 2.4 ± 1.1 years for major adverse cardiac events (MACE).[16] Thirty-six percent of patients had

CAC 0, and the absence of any plaque on coronary CTA was observed in 30%. By multivariable regression analysis, in a model containing coronary heart disease risk factors and CAC, CAC was the only significant predictor of MACE) ($P < .001$). When coronary CTA was added to the model, while CAC remained significant, the maximal stenosis severity grade, the number of vessels with obstructive CAD (≥50%), and the segment stenosis score were each independently and more strongly associated with cardiac events. The number of vessels with obstructive CAD was the strongest predictor of MACE ($P < .001$). There was significant upward risk reclassification by coronary CTA over the CAC score, even in the patients with CAC 0.

RANDOMIZED TRIALS

Evidence evaluating the utility of non-invasive testing among asymptomatic diabetic patients in randomized trials has been extremely limited, involving two trials involving SPECT-MPI and one trial involving coronary CTA. The first SPECT-MPI trial was the DIAD study.[26] In this study, 1143 asymptomatic diabetic patients were randomized to either a screening approach using SPECT-MPI (n = 522) or a non-imaging regimen. No treatment plan was specified in either group. While the prevalence of any perfusion or LV function abnormality was 22% in this study, a moderate-to-large ischemic perfusion defect was present in only 6%. During a mean follow-up of 4.8 years, the cardiac event rates were low. Overall, there was no outcome benefit in the group randomized to SPECT-MPI vs usual medical care. In the small group that did have moderate-to-large perfusion defects, the event rate was elevated (106).

The second randomized trial involving SPECT-MPI, the Basel Asymptomatic High-Risk Diabetes Outcome (BARDOT) trial,[27] studied 400 asymptomatic diabetic patients pre-selected at high a priori risk for clinical events. Patients underwent clinical evaluation and SPECT-MPI at baseline and again at 2 years. Patients with a normal SPECT-MPI study were assigned to usual medical care, while those with an abnormal SPECT-MPI study were randomly assigned on a 1:1 basis to intensive medication alone or medication plus invasive angiography, with revascularization if feasible. Baseline SPECT-MPI was abnormal in 22%, concordant with the results of the DIAD study, despite the selection of higher risk patients. The abnormal SPECT-MPI group had a higher frequency of overall cardiac events. In the 87 patients with abnormal SPECT-MPI, there was no difference in outcomes in those randomized to medical therapy only vs combined medical therapy and invasive angiography. This small trial, however, leaves unaddressed questions as to whether the benefit from SPECT or PET-MPI might be greater in even higher risk asymptomatic diabetic patients, possibly defined by high-risk CAC scores or abnormal coronary CTA findings.

The randomized trial involving coronary CTA was the FACTOR-64 trial which evaluated whether routine coronary CTA screening in asymptomatic diabetic patients affects changes in treatment that leads to a reduction in cardiac events.[28] Patients were randomized to either screening with coronary CTA with subsequent therapy directed by the imaging results or standard treatment. In patients with moderate stenosis (50-69%), stress imaging was recommended, and in those with severe stenosis (≥70%), invasive angiography was recommended, with the decision for revascularization left to the treating physician. In addition, within those randomized to CTA for those with any plaque or a CAC score ≥10 an intensive medical regimen with pre-specified aggressive treatment targets was recommended, while standard guidelines were recommended in the patients in the control arm. By the end of follow-up, the CTA group had achieved a greater reduction in CAD risk factors. There was also a tendency toward a lower overall event frequency of MACE in the CTA group, although the differences were modest, with absolute event rates being modest in both groups. Both increasing CAC abnormality and increasing CTA abnormality predicted a higher event rate in the group randomized to CTA.

Current Study

In this issue of the Journal, van den Hoogen et al[6] report their experience in the evaluation of 444 patients referred from a diabetes clinic for coronary CTA who were then followed up for cardiac events, defined as death, non-fatal MI, or late revascularization (>90 days after testing). The follow-up period was for a median of 5 years after CTA. Of the 444 patients, 431 had interpretable coronary CTA studies and 410 had CAC studies. Coronary CTA studies were categorized using standard categories (normal, non-obstructive, and 50-69% and ≥70% stenosis). Standard CAC categories were employed. During follow-up, 65 events occurred (14%), and 52 (80%) of these were late revascularizations. Of the revascularization events, only 52% were associated with new symptoms, while the remaining 48% occurred after an ischemic stress SPECT-MPI. There were no non-fatal myocardial infarctions.

The investigators reported a series of findings that are consistent with the emerging literature concerning atherosclerotic imaging in diabetics. First, as in other studies, there was a wide heterogeneity of atherosclerotic findings in this diabetic population. Among their patients, 15% had entirely normal coronary CTA examinations

(lower than the average prevalence reported in previous studies), 51% had non-obstructive CAD, 27% had moderate stenosis, and 7% had severe stenosis. This wide heterogeneity was also present in the results of CAC scanning, with 35% having CAC 0, and 26% CAC 1-99, 16% CAC 100-399, and 23% CAC $\geq$ 400.

Second, an increasing event rate was observed with increasing atherosclerotic burden: 3% in normal CTA, 5% in the non-obstructive, 33% in the moderate, and 40% in the severe stenosis groups over the 5-year period. Similar findings regarding the low-risk group were noted for CAC scanning, with the event rate of patients in the CAC 0 category being equal to the very low rate in those in the normal CTA group. By multivariable analysis, obstructive CAD provided incremental information for prediction of events over baseline variables, including the CAC score ($P = .001$). Of note, the authors also evaluated event rates by plaque type on CTA, observing that patients with events had more calcified and mixed plaques than the patients with no events. Interestingly, there was no difference in event rates according to the number of non-calcified plaques.

Third, the investigators noted a low overall event rate in their diabetic population, consistent with the growing recognition that modern aggressive medical management has substantially reduced event risk in diabetic patients. In fact, while the authors pointed out that some events might have occurred in other medical centers and missed in the study, there were no non-fatal myocardial infarctions in their diabetic population.

The analysis of outcomes in this study, however, is not without substantial limitation. Specifically, 80% of the composite cardiac events were late revascularizations—with half of these being in patients without new symptoms. The results of the CTA and their combination with ischemic SPECT-MPI findings undoubtedly contributed strongly to the high rate of revascularization events. Thus, as stated by the authors, conclusions regarding hard endpoints are not justified based on this study—there were only 13 hard events. Further, the observation of incremental prognostic information provided by the CTA findings of $\geq$50% stenosis over the CAC scan findings is likely to have been affected by post-test referral bias, with the CTA findings influencing the revascularization events.

As the authors also acknowledge, the study was not designed to assess the difference in prognostic performance between CTA and CAC scores. In this regard, it is noteworthy that the event rates in the CAC 0 group in this study were as low as those in the CTA normal group and that the number of non-calcified plaques was not predictive of cardiac events. Future study that would randomize patients to CAC scanning vs CTA in appropriately selected patient populations would be the best approach to assess this issue.

CONCLUSIONS

Several conclusions might be drawn from the literature and the current manuscript regarding cardiac CT in the asymptomatic patient. (1) Findings with cardiac CT have shown that a substantial proportion of asymptomatic patients have no evidence of coronary atherosclerosis: more than one-third have CAC 0 and approximately one-fourth have no plaque on coronary CTA. In these patients, the risk of cardiac events is exceedingly low. These findings would appear conclusive that diabetes per se should not be considered a CHD equivalent. (2) Defining the absence of a CHD equivalent in a substantial proportion of asymptomatic patients with diabetes has potential therapeutic implications. CAC scanning might be particularly relevant in the low-risk patients with diabetes. The absence of CAC in these patients might influence downscaling treatment and may be particularly relevant in the statin-intolerant patient. (3) A strategy based on coronary CTA in high-risk asymptomatic diabetic patients may have the potential to improve outcomes in these patients by leading to intensification of medical therapy or coronary revascularization. The results of the FACTOR-64 trial, while not reaching statistical significance, suggest that this strategy—including combination with ischemia assessment when results are borderline—might be associated with improved outcomes. (4) Whether CAC scanning without CTA—possibly in combination with ischemia testing—might provide an outcome benefit has not been tested and warrants evaluation.

Ultimately, outcome analyses must be combined with assessments of costs to assess the value of non-invasive testing strategies. However, extensive evidence results using cardiac CT in the asymptomatic patient with diabetes suggest that if the right patients are selected for testing—and if appropriate changes in therapy are applied after testing—a strategy of non-invasive testing with cardiac CT will prove to be of value.

Disclosure

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References

1. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: A collaborative meta-analysis of 102 prospective studies. Lancet 2010;375:2215-22.
2. Haffner SM, Lehto S, Ronnemaa T, Pyorala 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;339:229-34.
3. Bulugahapitiya U, Siyambalapitiya S, Sithole J, Idris I. Is diabetes a coronary risk equivalent? Systematic review and meta-analysis. Diabet Med 2009;26:142-8.
4. American Diabetes Association. Standards of medical care in diabetes—2013. Diabetes Care 2013;36:S11-66.
5. Perk J, De Backer G, Gohlke H, Graham I, Reiner Z, Verschuren M, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J 2012;33:1635-701.
6. van den Hoogen IJ, de Graaf MA, Roos CJ, et al. Prognostic value of coronary computed tomography angiography in diabetic patients without chest pain syndrome. J Nucl Cardiol. 2015. doi: 10.1007/s12350-015-0213-5.
7. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. JAMA 2012;308:788-95.
8. Joshi PH, Nasir K. Discordance between risk factors and coronary artery calcium: Implications for guiding treatment strategies in primary prevention settings. Prog Cardiovasc Dis 2015. doi: 10.1016/j.pcad.2015.05.006.
9. Erbel R, Mohlenkamp S, Moebus S, Schmermund A, Lehmann N, Stang A, et al. Coronary risk stratification, discrimination, and reclassification improvement based on quantification of subclinical coronary atherosclerosis: The Heinz Nixdorf Recall study. J Am Coll Cardiol 2010;56:1397-406.
10. Budoff MJ, Mohlenkamp S, McClelland R, Delaney JA, Bauer M, Jockel HK, et al. A comparison of outcomes with coronary artery calcium scanning in unselected populations: The Multi-Ethnic Study of Atherosclerosis (MESA) and Heinz Nixdorf RECALL study (HNR). J Cardiovasc Comput Tomogr 2013;7:182-91.
11. Raggi P, Shaw LJ, Berman DS, Callister TQ. Prognostic value of coronary artery calcium screening in subjects with and without diabetes. J Am Coll Cardiol 2004;43:1663-9.
12. Malik S, Budoff MJ, Katz R, Blumenthal RS, Bertoni AG, Nasir K, 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.
13. Moebus S, Stang A, Mohlenkamp S, Dragano N, Schmermund A, Slomiany U, et al. Association of impaired fasting glucose and coronary artery calcification as a marker of subclinical atherosclerosis in a population-based cohort-results of the Heinz Nixdorf Recall Study. Diabetologia 2009;52:81-9.
14. Yeboah J, Erbel R, Delaney JC, Nance R, Guo M, Bertoni AG, et al. Development of a new diabetes risk prediction tool for incident coronary heart disease events: The Multi-Ethnic Study of Atherosclerosis and the Heinz Nixdorf Recall Study. Atherosclerosis 2014;236:411-7.
15. Silverman MG, Blaha MJ, Budoff MJ, Rivera JJ, Raggi P, Shaw LJ, et al. Potential implications of coronary artery calcium testing for guiding aspirin use among asymptomatic individuals with diabetes. Diabetes Care 2012;35:624-6.
16. Min JK, Labounty TM, Gomez MJ, Achenbach S, Al-Mallah M, Budoff MJ, et al. Incremental prognostic value of coronary computed tomographic angiography over coronary artery calcium score for risk prediction of major adverse cardiac events in asymptomatic diabetic individuals. Atherosclerosis 2014;232:298-304.
17. Park GM, Lee SW, Cho YR, Kim CJ, Cho JS, Park MW, et al. Coronary computed tomographic angiographic findings in asymptomatic patients with type 2 diabetes mellitus. Am J Cardiol 2014;113:765-71.
18. Kamimura M, Moroi M, Isobe M, Hiroe M. Role of coronary CT angiography in asymptomatic patients with type 2 diabetes mellitus. Int Heart J 2012;53:23-8.
19. Roos CJ, Kharagjitsingh AV, Jukema JW, Bax JJ, Scholte AJ. Comparison by computed tomographic angiography-the presence and extent of coronary arterial atherosclerosis in South Asians versus Caucasians with diabetes mellitus. Am J Cardiol 2014;113:1782-7.
20. Scholte AJ, Schuijf JD, Kharagjitsingh AV, Dibbets-Schneider P, Stokkel MP, Jukema JW, et al. Different manifestations of coronary artery disease by stress SPECT myocardial perfusion imaging, coronary calcium scoring, and multislice CT coronary angiography in asymptomatic patients with type 2 diabetes mellitus. J Nucl Cardiol 2008;15:503-9.
21. Silva JD, Mota P, Coelho A, Catarino R, Leitao-Marques A. Incidence of subclinical atherosclerosis in asymptomatic type-2 diabetic patients: The potential of multi-slice computed tomography coronary angiography. Coron Artery Dis 2011;22:26-31.
22. Rivera JJ, Nasir K, Choi EK, Yoon YE, Chun EJ, Choi SI, et al. Detection of occult coronary artery disease in asymptomatic individuals with diabetes mellitus using non-invasive cardiac angiography. Atherosclerosis 2009;203:442-8.
23. Loffroy R, Bernard S, Serusclat A, Boussel L, Bonnefoy E, D'Athis P, et al. Noninvasive assessment of the prevalence and characteristics of coronary atherosclerotic plaques by multidetector computed tomography in asymptomatic type 2 diabetic patients at high risk of significant coronary artery disease: A preliminary study. Arch Cardiovasc Dis 2009;102:607-15.
24. Park GM, Lee JH, Lee SW, Yun SC, Kim YH, Cho YR, et al. Comparison of coronary computed tomographic angiographic findings in asymptomatic subjects with versus without diabetes mellitus. Am J Cardiol 2015;116:372-8.
25. Rozanski A, Gransar H, Shaw L, et al. Comparison of the atherosclerotic burden among asymptomatic patients vs matched volunteers. J Nucl Cardiol 2011;291-8.
26. Wackers FJ, Young LH, Inzucchi SE, Chyun DA, Davey JA, Barrett EJ, et al. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: The DIAD study. Diabetes Care 2004;27:1954-61.
27. Zellweger MJ, Maraun M, Osterhues HH, Keller U, Muller-Brand J, Jeger R, et al. Progression to overt or silent CAD in asymptomatic patients with diabetes mellitus at high coronary risk: Main findings of the prospective multicenter BARDOT trial with a pilot randomized treatment substudy. JACC Cardiovasc Imaging 2014;7:1001-10.
28. Muhlestein JB, Lappe DL, Lima JA, Rosen BD, May HT, Knight S, et al. 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. JAMA 2014;312:2234-43.