^{18}F-Sodium Fluoride Imaging of Coronary Atherosclerosis in Ambulatory Patients With Diabetes Mellitus

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Objective—Although patients with diabetes mellitus (DM) are considered at high risk of cardiovascular events, there is growing evidence that this notion is incorrect. Atherosclerosis imaging may identify patients at risk.

Approach and Results—We performed coronary atherosclerosis with ^{18}F-sodium fluoride (NaF) positron emission tomography/computed tomography and gated chest computed tomography for coronary artery calcium in 88 consecutive ambulatory patients with DM on a stable medical regimen. NaF has been shown to localize avidly in culprit lesions of patients with acute coronary syndromes and may identify unstable plaques. NaF activity was measured as target (coronary arteries)-to-background (left ventricular pool) ratio (TBR). High TBR was defined as ≥1.5. The mean age of the cohort was 54±14 years, 55% had type 2 DM, 65% were men, the median HgbA1c (hemoglobin A1c) and LDL (low-density lipoprotein) cholesterol were 7.5% (interquartile range, 7.1–8.5) and 1.9 mmol/L (interquartile range, 1.5–2.6), respectively. Mean coronary artery calcium score was 374±773, and median TBR was 1.2. Coronary artery TBR ≥1.5 was detected in 13 (15%) patients. In univariable analyses, male sex (P=0.0002), estimated glomerular filtration rate (P=0.02), and total coronary artery calcium score (P=0.04) were associated with TBR. In multivariable analyses, TBR >median was associated with male sex (P=0.0001) and statin use (P=0.042).

Conclusions—In ambulatory patients with DM asymptomatic for cardiovascular disease, the prevalence of potentially vulnerable plaques detected with NaF was low, but in the absence of follow-up data at this stage, we cannot assess the import of this information. Future research will establish whether NaF imaging helps risk stratify patients with DM.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT03530176.

Visual Overview—An online visual overview is available for this article. **(*Arterioscler Thromb Vasc Biol*. 2019;39:276-284. DOI: 10.1161/ATVBAHA.118.311711.)**

Key Words: atherosclerosis ■ diabetes mellitus ■ follow-up studies ■ humans ■ prevalence

The lifetime risk of cardiovascular events in patients with diabetes mellitus (DM) is 2-fold higher than for subjects of similar age and sex but without DM.[1] However, the notion that DM should be considered a coronary artery disease risk equivalent[2] and that all patients with DM are universally at high risk has been challenged in several studies.[3–5] Germane to proper implementation of prevention therapies is an accurate stratification of subjects at risk, and imaging may offer a means to improve such a task. Several professional organizations issued guidelines and position statements on screening for cardiovascular disease in DM, but overall support in favor of atherosclerosis imaging is not strong.[6] The main reasons for the weak support are the lack of a strong association between imaging findings and outcome, the paucity of interventions on such imaging findings that may reduce subsequent events, and the risks associated with radiation exposure for some techniques. ^{18}F-sodium fluoride (NaF) is a tracer used in positron emission tomographic (PET) imaging to detect malignant bone metastases. NaF was also shown to selectively deposit in atherosclerotic plaques where microcalcifications accumulate in crystals of calcium apatite.[7–9] Joshi et al[10] showed that culprit lesions accumulate NaF avidly in the course of an acute coronary syndrome or after an acute cerebrovascular event. This elicited our interest in the use of NaF PET imaging to potentially identify patients with DM who may harbor plaques at risk of rupture. We, therefore, designed a study in asymptomatic and ambulatory patients with DM, generally considered to be at high cardiovascular risk, to evaluate the prevalence and extent of coronary artery NaF uptake. We further performed dedicated computed tomography (CT) scans to assess the extent of coronary artery calcium (CAC), to correlate the extent of NaF with the severity of this established marker of atherosclerotic risk.

See accompanying editorial on page 124

Methods

The data that support the findings of this study are available from the corresponding author on reasonable request.

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Nonstandard Abbreviations and Acronyms	
CAC	coronary artery calcium
CT	computed tomography
DM	diabetes mellitus
FRS	Framingham risk score
HDL	high-density lipoprotein
HgbA1c	hemoglobin A1c
LDL	low-density lipoprotein
NaF	sodium fluoride
PET	positron emission tomography
SGLT2i	sodium-glucose transporter 2 inhibitor
SUV	standard uptake value
TBR	target-to-background ratio
UKPDS	United Kingdom Prospective Diabetes Study

Patient Selection

The study was approved by the Ethical Review Board at the University of Alberta, and the investigators obtained dispensation from Canada Health to use NaF for the unapproved indication of arterial imaging to conduct this study. The study was registered at http://www.clinicaltrails.gov (clinical trial identifier, NCT03530176). Ninety-five adult, consecutive ambulatory patients with an established diagnosis of either type 1 or type 2 DM were enrolled from internal medicine and endocrinology clinics. Of these, 88 completed both the PET/CT and CAC studies. The clinical characteristics of the 7 patients who did not complete both PET/CT and CAC were similar to those who completed them. The reasons for incomplete study participation were: claustrophobia (n=1), failing to return for PET imaging (n=1), and failure to return for CT scan imaging (n=5). All patients were ambulatory and were receiving optimal medical therapy with stable doses (at least 6 months without changes) of antihyperglycemic, lipid-lowering, and blood pressure-lowering drugs. No patient had a history of recent myocardial infarction, angina, or chest pain. Information on traditional risk factors for atherosclerotic heart disease, history of retinopathy, history of atherosclerotic cardiovascular disease (myocardial infarction, percutaneous coronary intervention, coronary artery bypass surgery, transient ischemic attacks, stroke, and amputations), and current medications was collected via a questionnaire provided at the time of the enrollment visit and complemented by review of the patients' medical records. Laboratory test results obtained within 90 days of PET/CT imaging for serum total cholesterol, LDL (low-density lipoprotein) and HDL (high-density lipoprotein) cholesterol, HgbA1c (hemoglobin A1c), and serum creatinine levels were obtained via review of the electronic health records of each patient. Resting heart rate and blood pressure were measured in the seated position at the time of PET/CT imaging. The estimated glomerular filtration rate was calculated using the Modification of Diet in Renal Disease formula (https://www.niddk.nih.gov/health-information/communication-programs/nkdep/laboratory-evaluation/glomerular-filtration-rate/estimating; last accessed on August 3, 2018). The Framingham risk score (FRS) was calculated using the formula found at https://www.framinghamheartstudy.org/fhs-risk-functions/hard-coronary-heart-disease-10-year-risk (last accessed on August 3, 2018) based on the Adult Treatment Panel III formula.[11] All patients gave written informed consent to participate in the study, and the study was conducted according to the Declaration of Helsinki for research in human subjects (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/; last accessed on July 18, 2018).

Imaging Acquisition and Interpretation

CT for CAC

All patients underwent a gated CT of the chest to measure CAC. CT imaging was done with a 64-slice CT scanner (Somatom Definition; Siemens, Erlangen, Germany), and examinations were performed in flash mode (single heart beat acquisition taking 250–350 ms) from the bronchial carina to the diaphragm. Image data were reconstructed in sequential 3 mm slices, and the CAC score was calculated offline according to the Agatston method[12] and volume method[13] on a dedicated workstation (TeraRecon; Medical Imaging Viewing Solutions, Foster City, CA). Because the statistical results did not differ when we used the Agatston or volume score in the analyses, for ease of interpretation in this manuscript, we report the Agatston score only. CAC scores were calculated for individual coronary arteries and as a combined global score.

PET with NaF

After injection of 370 MBq (10 mCi) of NaF patients relaxed for 1 hour in a semidarkened room before imaging. All examinations were performed on a PET/CT system (Philips Gemini TF; Eindhoven, the Netherlands) with PET images obtained in a single bed position over the heart (20-minute ECG-gated list-mode PET acquisition). Matching CT data were acquired using a 16-slice multidetector CT during quiet breathing (0.5 seconds per rotation, 100 mAs tube current, and 120 kVp tube voltage). CT data were reconstructed in 3 mm thick slices with no overlap. PET data were obtained in 3-dimensional mode with time-of-flight corrections applied. Iterative reconstruction (RAMLA) with 4 mm isotropic voxels using CT-based attenuation correction was used. The global estimated radiation dose absorbed by each patient varied between 4 and 6 mSv. The PET/CT and gated chest CT scans for CAC scoring in the majority of cases were performed the same day and in 10 patients within 5 days of each other.

Image Analysis

All images were reviewed using Oasis workstations (Segami Corporation, Columbia, MD). The PET images were scaled with an upper standard uptake value (SUV) threshold of 2.0 and lower threshold of 0.0 for review. The PET-only images, CT-only images, and fused PET/CT images were reviewed synchronously in multiple planes. The left main coronary artery, left anterior descending coronary artery, left circumflex coronary artery, and right coronary artery were assessed independently. The SUV max was measured for the most NaF avid focus for each artery. If no focus was identified visually, then the SUV max of the proximal portion of the artery was obtained. For comparative blood pool measurements, we measured the SUV mean and SUV max of the left ventricle blood pool. A 2-cm diameter spherical volume of interest was placed within the left ventricle, avoiding myocardium, cardiac valves, and papillary muscles. The superior vena cava blood pool was also measured; however, these data were not included in the analyses because of obvious spillover of activity from the adjacent aortic wall in many patients. Target-to-background ratio (TBR) was calculated as SUV max (coronary)/SUV mean (left ventricular blood pool). A TBR of ≥1.5 was considered abnormal as reported before.[8] To confirm the validity of this approach, we calculated the ratio of SUVmax/SUVmean of all blood pool measurements we performed. This ratio can be considered a measure of variability because of image noise, and its maximum value was 1.43. Therefore, a TBR of 1.5 is a reasonable cutoff to identify lesions with activity above the background range of blood pool noise.

Statistical Analysis

The patients were divided into quartiles of TBR, and descriptive analyses of demographic, clinical, and imaging characteristics were performed based on quartiles of TBR. Among the 88 patients in the dataset, there were clusters of patients with identical TBR; therefore, the number of patients in each quartile of TBR is not exactly a quarter of 88. The mean (SD) of continuous variables were compared across quartiles of TBR using univariable ANOVA. One-way ANOVA assumes that continuous variables have a normal distribution, and the group variances are identical. Medians of non-normally distributed continuous variables were compared across quartiles of TBR using Kruskal-Wallis test. This test is the nonparametric alternative to 1-way ANOVA. Percentages for categorical variables were compared with the χ^2 test. Multivariable logistic regression was used to assess predictors of TBR >median using the following variables: age, sex,

LDL-C, HgbA1c, total Agatston score, estimated glomerular filtration rate, use of statins, duration of DM, use of insulin, and history of cardiovascular disease. Statistical significance was set at $P < 0.05$.

Results

The clinical and demographic characteristics of the 88 patients who completed the study are shown in Table 1. The population was predominantly white (85%), middle aged (54±14 years old), with a majority of men (65%), and with a slight majority of patients with type 2 DM (55%). A minority had a history of cardiovascular disease (22.7%). The patients had a long history of DM before enrollment in the study (median, 15 years), had a fair glycemic control (mean HgbA1c of 7.9±1.3%), and an LDL-C level close to 2 mmol/L (mean, 2.1±0.9 mmol/L; median, 1.9 mmol/L; interquartile range, 1.5–2.6)—the level recommended by the Canadian Guidelines on lipid treatment.[14] The FRS calculated independent of the presence of DM was low, average of 6±6%. The FRS of course would have been high in every patient if DM was considered a cardiovascular disease risk equivalent as recommended by the Adult Treatment Panel III algorithm.[9]

Among the 88 study patients, 25 (28%) had no CAC on gated chest CT scans. However, the mean and median CAC scores of those with coronary calcium were high compared with the general population. The mean cohort Agatston score of 374 corresponds to the 95th percentile for a middle-aged white man and the 99th percentile for a middle-aged white woman according to the MESA (Multi Ethnic Study of Atherosclerosis) calculator (https://www.mesa-nhlbi.org/Calcium/input.aspx; last accessed on August 3, 2018). Even the lowest quartile of TBR had a high CAC score compared with the general population (88th and 98th percentile for a white man and woman, respectively). Figure 1 shows a plot of FRS and CAC scores across quartiles of TBR.

The median NaF coronary artery TBR was 1.2, and a high TBR (≥1.5) was detected in 13 of 88 patients (15%). The histogram on Figure 2 shows a distribution of the detected TBRs along the coronary artery tree of the study patients. The characteristics of the 13 patients with elevated TBR are shown in Table 2. Four of 13 patients showed high NaF activity without colocalized CAC. Notably, 3 of these patients had a high TBR in the left main coronary artery trunk in the absence of CAC in the same vessel, although they had CAC in other vessels. The remaining 9 patients showed calcification in the same vessel where high NaF uptake was detected, as well as other vessels. Figure 3 shows a focus of high uptake of NaF in the midsection of the left anterior descending coronary artery in correspondence with a calcified plaque. Figure 4 shows avid NaF uptake in the aortic root where there is no visible calcium but no NaF uptake in the heavily calcified left main and left anterior descending coronary artery.

On univariate analysis, male sex, estimated glomerular filtration rate, and total Agatston score were significantly different between quartiles of TBR. Given the small number of patients with an elevated TBR (≥1.5), we could not perform a multivariable logistic regression analysis to identify predictors of high TBR. We, therefore, investigated which variables were associated with a TBR >median (1.2). Among the variables selected, only male sex (P=0.0001) and use of statins (P=0.004) were associated with TBR >1.2.

Discussion

In this study, we used molecular imaging with NaF PET/CT and gated CT for CAC scoring, to investigate the prevalence and extent of coronary atherosclerosis in stable, ambulatory patients with DM. The prevalence of high NaF uptake—a putative marker of plaque instability—was low in the coronary artery tree of the patients studied, although in the absence of outcome data, it is difficult to assess the clinical significance of this finding. There was a univariate association between male sex, estimated glomerular filtration rate, and total calcium score with high TBR, but none of the other risk factors showed an association. In line with prior publications, a sizeable proportion of patients (28%) did not have any detectable CAC.[15] The prognosis for these patients has been reported to be excellent and similar to that of the general population.[15,16] On average, however, our predominantly white population had a high calcium score. Hence, our patients had evidence of moderate-to-severe coronary atherosclerosis, but there was little evidence of activity within the calcified areas or elsewhere in the coronary artery tree. Our observation that NaF uptake may be associated with statin use in multivariable logistic analyses is interesting and can be interpreted in several ways: either the patients receiving statins were considered at higher cardiovascular risk by the treating physicians or, as shown in sequential studies, statins promote vascular calcification[17–20] and potentially promote NaF uptake. The 2 options could also coexist.

Our study focuses on NaF imaging in a sizeable number of patients with DM. Prior studies in either volunteers,[21] or patients with stable[22,23] and unstable[8] coronary artery disease, enrolled a maximum of 17 patients with DM, and no information was provided on the NaF findings in these specific patients. Therefore, we believe that our data add valuable information to the imaging literature of patients with DM. In view of the high cardiovascular risk of patients affected by DM, investigators have been interested in applying imaging modalities to search for patients at greater risk of events. The DIAD trial (Detection of Ischemia in Asymptomatic Diabetics) failed to prove that searching for coronary artery lesions causing myocardial ischemia improves survival.[24] The more recent FACTOR 64 trial failed to show that an approach based on coronary CT angiography to diagnose coronary luminal stenoses is superior to an approach based on functional stress testing.[25] Surprisingly, the prevalence of severe disease was not high in either the DIAD or FACTOR 64 trial, and the observed mortality and morbidity were lower than expected. In addition, Chhabra et al[26] recently reported a substantial reduction in the incidence of abnormal nuclear stress tests in symptomatic patients with DM. One wonders if a more aggressive management of risk factors or an inappropriately liberal use of stress testing is the root cause of such phenotypic change. Our results support the notion that well-managed, ambulatory patients with DM are indeed at low risk of events as recently shown by Rawshani et al.[27] We cannot exclude that we might have detected a larger burden of disease with other markers of plaque instability. In fact, basic science evidence shows that inflammation and calcification proceed in parallel,[28–30] and detecting inflammation in the arterial wall may be more informative and prognostically significant than NaF imaging.

Table 1. Clinical and Demographic Characteristics of 88 Ambulatory Patients With Diabetes Mellitus

Variable Label		First Quartile	Second Quartile	Third Quartile	Fourth Quartile	Total	*P* Value
TBR		≤1.1	1.11–1.2	1.21–1.375	>1.375		
Total, n		23	18	26	21	88	
Age, y	Mean (SD)	55.5 (12.9)	50.9 (15.5)	50.4 (14.1)	59.3 (12.4)	54.0 (14.0)	0.1146
	Median (IQR)	58.0 (47.0–66.0)	51.0 (47.0–62.0)	52.5 (41.0–60.0)	62.0 (54.0–67.0)	56.5 (47.0–65.5)	0.0992
Sex							
Men	n (%)	8/23 (34.8)	9/18 (50.0)	22/26 (84.6)	18/21 (85.7)	57/88 (64.8)	0.0002
Women	n (%)	15/23 (65.2)	9/18 (50.0)	4/26 (15.4)	3/21 (14.3)	31/88 (35.2)	
Type 2 DM	%	52	67	40	65	55	0.2458
LDL-C, mmol/L	Mean (SD)	2.0 (0.7)	2.1 (1.0)	2.4 (1.1)	1.9 (0.9)	2.1 (0.9)	0.2866
	Median (IQR)	2.0 (1.6–2.5)	1.6 (1.5–2.6)	2.4 (1.8–3.1)	1.8 (1.4–2.3)	1.9 (1.5–2.6)	0.2211
HgbA1c, %	Mean (SD)	7.7 (1.0)	7.4 (0.7)	8.1 (1.6)	8.2 (1.4)	7.9 (1.3)	0.2503
	Median (IQR)	7.4 (7.1–8.5)	7.6 (7.1–7.9)	7.7 (7.2–8.7)	8.2 (7.0–9.2)	7.5 (7.1–8.5)	0.577
eGFR, mL/min per 1.73 m2	Mean (SD)	75.7 (23.5)	90.8 (22.0)	88.3 (22.9)	71.1 (27.0)	81.6 (24.9)	0.0234
	Median (IQR)	77.0 (58.0–93.0)	86.5 (76.0–108.0)	91.0 (72.0–101.0)	69.0 (49.0–94.0)	86.0 (67.0–99.0)	0.0487
Duration of DM, y	Mean (SD)	18.3 (14.3)	16.6 (13.6)	20.8 (16.4)	20.1 (14.9)	19.1 (14.8)	0.8074
	Median (IQR)	15.0 (6.0–26.0)	11.5 (7.0–24.0)	17.0 (8.0–31.0)	14.5 (9.0–35.0)	15.5 (7.5–30.5)	0.834
Smoking							
Never	n (%)	13 (65.0)	16 (88.9)	16 (64.0)	13 (65.0)	58 (69.9)	0.4573
Current	n (%)	2 (10.0)	1 (5.6)	5 (20.0)	4 (20.0)	12 (14.5)	
Past smoker	n (%)	5 (25.0)	1 (5.6)	4 (16.0)	3 (15.0)	13 (15.7)	
Hypertension	n (%)	9 (42.9)	7 (38.9)	11 (44.0)	15 (75.0)	42 (50.0)	0.0829
Insulin+OHA	n (%)	4/21 (19.0)	3/18 (16.7)	9/25 (36.0)	2/20 (10.0)	18/84 (21.4)	0.1705
Insulin only	n (%)	8/21 (38.1)	5/18 (27.8)	11/25 (44.0)	7/20 (35.0)	31/84 (36.9)	0.7462
OHA only	n (%)	7/21 (33.3)	9/18 (50.0)	5/25 (20.0)	11/20 (55.0)	32/84 (38.1)	0.0664
Statin use	n (%)	14/23 (60.9)	12/18 (66.7)	11/26 (42.3)	12/21 (57.1)	49/88 (55.7)	0.3865
Previous laser for retinopathy	n (%)	2 (9.5)	2 (11.1)	5 (20.0)	4 (20.0)	13 (15.5)	0.6742
	n (%)	2/21 (9.5)	4/18 (22.2)	8/25 (32.0)	5/20 (25.0)	19/84 (22.6)	0.3365
Total CAC Agatston score	Mean (SD)	182.7 (313.2)	142.3 (253.3)	347.8 (813.1)	774.9 (1122.1)	374.6 (773.3)	0.0426
	Median (IQR)	0.6 (0.0–437.0)	3.3 (0.0–203.8)	25.4 (0.0–135.3)	228.5 (60.0–925.6)	49.0 (0.0–429.0)	0.0083
Framingham risk score, % (10 y risk)	Mean (SD)	5.1 (6.1)	4.6 (3.5)	6.5 (6.5)	7.5 (6.0)	5.9 (5.7)	0.5117
	Median (IQR)	2.3 (0.4–7.5)	3.9 (1.7–8.9)	4.2 (1.6–7.9)	6.0 (2.1–11.5)	4.2 (1.5–9.2)	0.4718
Prior ASCVD	n (%)	5 (22)	1 (5.6)	8 (31)	6 (28.6)	20 (22.7)	0.2213

ASCVD indicates atherosclerotic cardiovascular disease; CAC, coronary artery calcium; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HgbA1c, hemoglobin A1c; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; OHA, oral hypoglycemic agents; and TBR, target-to-background ratio.

However, imaging of the coronary arteries with a tracer more specific for inflammation, such as ^{18}F-fluoro-deoxyglucose is known to be poor because of myocardial spillover and image contamination.[10,19] Although the new ^{68}gallium-based tracer DOTATATE has been shown to have good sensitivity and specificity for detection of inflammation in atherosclerotic plaques of patients with acute coronary syndromes,[31] nothing is known of its utility for screening in the general population and patients with DM.

CAC scores have been reported to be higher in patients with DM than in the general population of the same age and sex and have been shown to provide good discrimination of risk for all-cause mortality, although as many as 30% of patients with DM have no CAC.[16,32] The imaging council of the American College of Cardiology recently recommended an initial CAC screening of patients with DM, complemented by stress testing in symptomatic patients or patients at higher risk (such as patients with an abnormal ECG or peripheral vascular disease).[33] The American Diabetes Association (http://www.ndei.org/ADA-diabetes-management-guidelines-cardiovascular-disease-CVD-management-lipids-BP.aspx.html; last accessed on August 1, 2018) recommends against

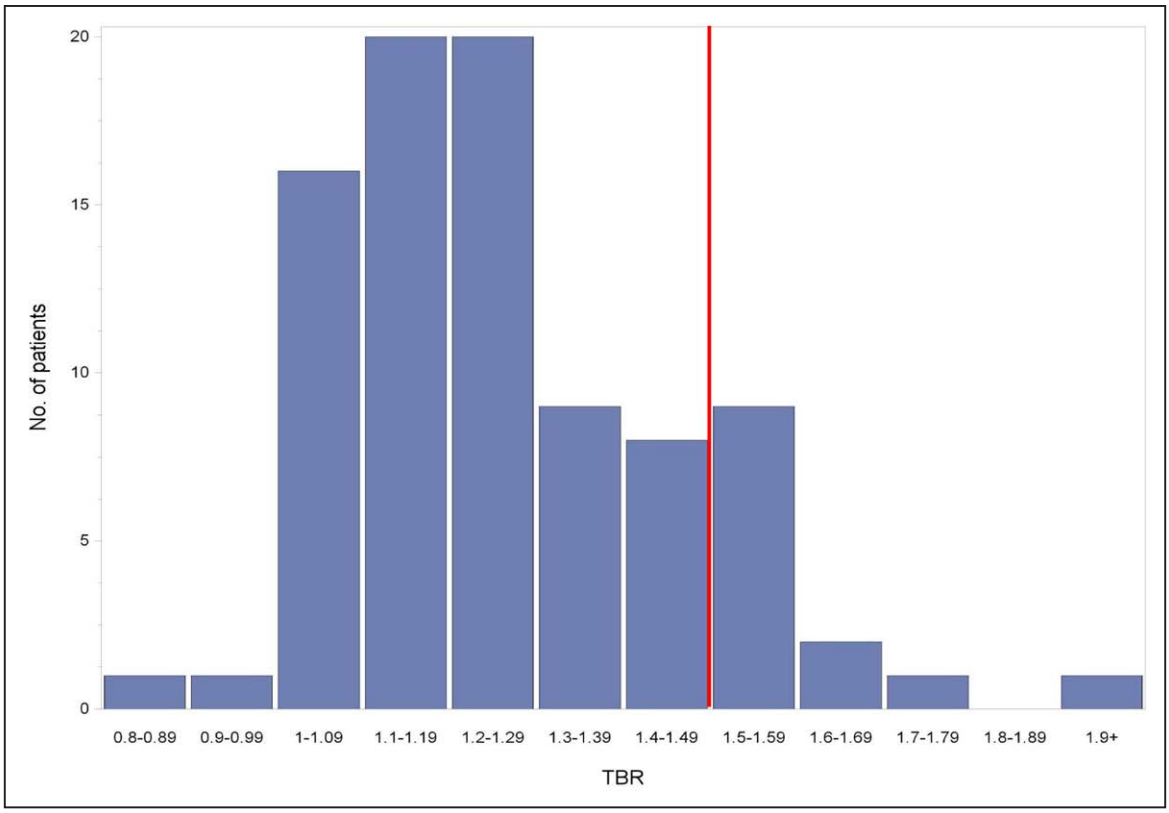

Figure 1. Histogram of target-to-background ratio (TBR) distribution in the study population.

screening with imaging unless symptoms or electrocardiographic signs of coronary artery disease are present. However, the majority of ambulatory patients with DM are asymptomatic and do not present objective signs of cardiovascular disease. Hence, the pressing question remains: How do we identify patients at higher risk? Our middle-aged

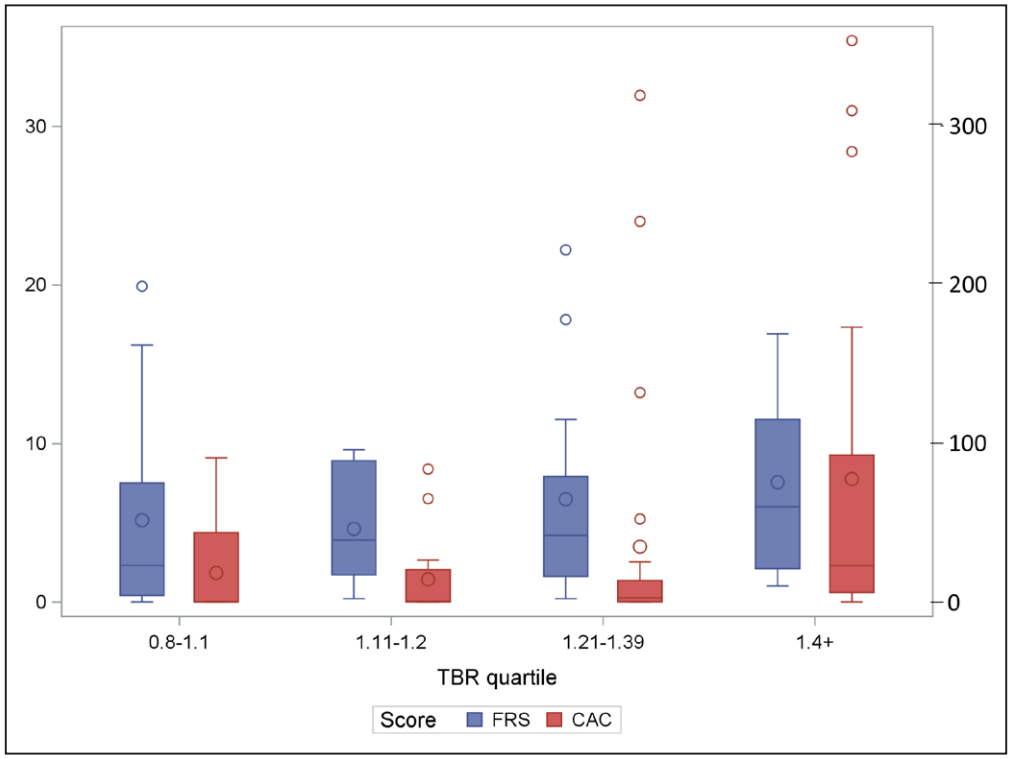

Figure 2. Box plot of Framingham risk score (FRS) and coronary artery calcium (CAC) score by quartile of target-to-background ratio (TBR).

Table 2. Clinical Characteristics of Patients With Diabetes Mellitus and High Coronary Artery ^{18}F-Sodium Fluoride Uptake

Patient No.	1	2	3	4	5	6	7	8	9	10	11	12	13
Age, y	81	36	26	53	60	52	68	69	75	57	62	62	46
Sex	M	M	M	M	F	M	M	F	M	F	M	M	M
DM type	2	1	1	2	1	2	2	2	2	1	2	2	1
Duration of DM, y	20	27	22	5	47	2	12	10	14	45	15	10	33
HgbA1c, %	6.6	7.2	9.2	9.4	9.2	10.0	9.9	7.1	7.2	8.5	6.1	8.6%	9.2
LDL-C, mmol/L	1.3	1.9	1.9	3.0	1.6	0.9	2.3	1.3	NA	1.3	2.8	2.6	1.8
Smoking	y	y	n	y	n	n	n	n	n	n	n	n	n
Hypertension	y	y	n	n	n	y	y	y	y	y	y	y	y
Dyslipidemia	y	n	n	y	n	n	y	y	y	n	n	n	y
History of ASCVD	y	y	n	n	y	n	n	n	y	y	n	n	n
BMI	NA	24	20	NA	25	42	38	34	42	25	37	38	28
Statins	Y	N	N	N	Y	Y	Y	Y	Y	Y	N	Y	Y
eGFR	48	10	94	47	57	99	64	91	26	97	90	95	65
Artery with high TBR	LM	LM	LM	LM	LM	LM	LM, LAD	LM, LAD	LAD	LAD	LAD	LAD	LAD
TBR in LM	1.75	1.50	1.50	1.57	1.50	1.50	2.00	1.50					
TBR in LAD							1.63	1.63	1.55	1.50	1.50	1.67	1.50
LM CAC score	170	0	0	0	14.4	105	8	2.8	0	0	0	0	0
LAD CAC score							70	397	1256	0	295	339	18
Total CAC score	3098	927	0	2.1	3540	441	78	922	2839	0	710	429	32

ASCVD indicates atherosclerotic cardiovascular disease; BMI, body mass index; CAC, coronary artery calcium; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; F, female; HgbA1c, hemoglobin A1c; LAD, left anterior descending coronary artery; LDL-C, low-density lipoprotein cholesterol; LM, left main trunk; M, male; NA, not available; and TBR, target-to-background ratio.

patients exhibited a fair glycemic control and LDL-C level, and only a few had a history of atherosclerotic cardiovascular disease. Surprisingly, just >50% received statins, although a substantial proportion of our subjects had type 1 DM where the recommendation for statin therapy is grade D by consensus.[34] As presented, our findings suggest that a clinically stable, metabolically well-controlled, middle-aged population with DM may not be at high risk solely on the basis of the diagnosis of DM.[35] Continued efforts to develop better tools to identify high-risk asymptomatic patients with DM are extremely important given the increasing incidence and prevalence of this disease and its associated high lifetime risk of cardiovascular events. However, the high cardiovascular risk of patients with DM is not limited to development of atherosclerotic complications. In fact, recent studies have demonstrated early and striking reductions in cardiovascular mortality and hospitalization for heart failure with the use of SGLT2i (sodium-glucose transporter 2 inhibitors) in people with type 2 DM.[36,37] These findings have generally been attributed to volume reduction, the antioxidant effects of SGLT2i, and prevention of fatal arrhythmias.[38] Thus, the excess cardiovascular mortality attributable to atherosclerotic disease in patients with DM may have been overestimated in the past.

There were a number of limitations in our study. Ours was a cross-sectional and relatively small study, although it included several-fold more patients with DM than prior reports on NaF. We had no controls from the general population to assess the prevalence of NaF uptake in subjects of similar age and sex; however, given the radiation exposure with NaF, it would have been unethical to expose healthy individuals to this type of imaging. Our patients were fairly young and healthy, and our findings cannot be exported directly to other populations. We did not perform CT angiography, which would have allowed a more precise registration of radioactivity and coronary artery plaques. The PET/CT equipment we used may be less sensitive than more modern scanners available in the market, although our equipment is similar to that used in prior seminal investigations with NaF. We did not use motion correction during PET imaging, although gating in a small sample of our patients did not change the results even minimally (data not shown). The majority of our patients were receiving metformin and sulfanilureas, with 11 patients receiving a DDP4i and only 3 patients receiving a glitazone and 2 patients receiving an SGLT2i. Whether these drugs had any procalcifying or anticalcifying effect is unknown at this time. Finally, there remains an urgent need to standardize NaF reporting because some investigators favor SUV, whereas others favor TBR although there is no set value for TBR that is known to be associated with higher risk. The TBR level we chose has been used in the past to define high tracer uptake, but there are no prospective outcome trials that used that threshold. In the publication by Joshi et al[10] the median TBR in culprit arteries of patients with acute coronary syndromes was 1.66 with an interquartile range of 1.4 to 2.25; hence a wide variability.

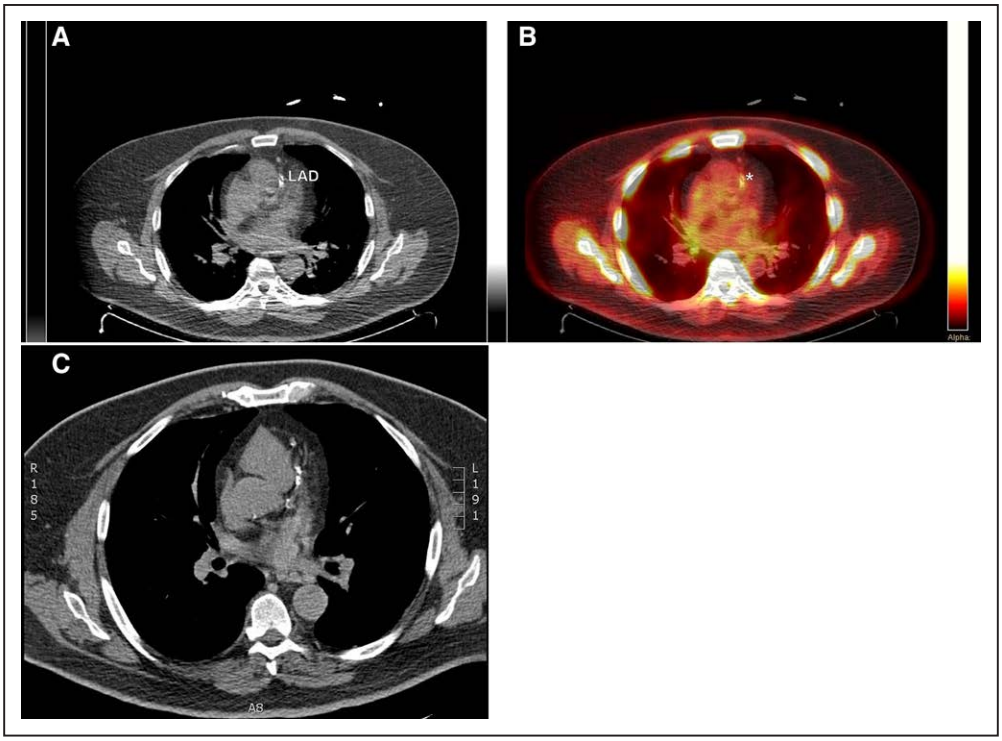

Figure 3. Low-resolution attenuation computed tomographic scan of the chest showing calcification in the mid-left anterior descending coronary artery (**A**). Fused positron emission tomography/computed tomography images showing uptake of ^{18}F-sodium fluoride (identified by the asterisk) in the mid section of the left anterior descending (LAD) coronary artery matching the calcified plaque seen on the attenuation chest computed tomographic scan (**B**). The high-resolution gated chest computed tomographic scan confirms the presence of several areas of calcification along the course of the LAD coronary artery (**C**).

In conclusion, the search for better tools for risk estimation in DM continues. A recent publication showed that 5 different risk-assessment algorithms based on clinical characteristics alone failed to identify risk accurately.[39] A prior investigation showed that the addition of information provided by anatomic atherosclerosis imaging (CAC and carotid intima media thickness) improved risk discrimination in patients with DM compared with the FRS and the UKPDS (United Kingdom Prospective Diabetes Study) risk score.[40] Therefore, imaging may have a role in improving risk stratification of patients with DM. However, in view of the cost and radiation exposure inherent with NaF and CAC imaging and the lack of outcome data at this time, NaF PET/CT does not seem to be an optimal method to screen for the presence of vulnerable plaques in ambulatory, asymptomatic patients with DM. Future studies will be needed to investigate the prognostic

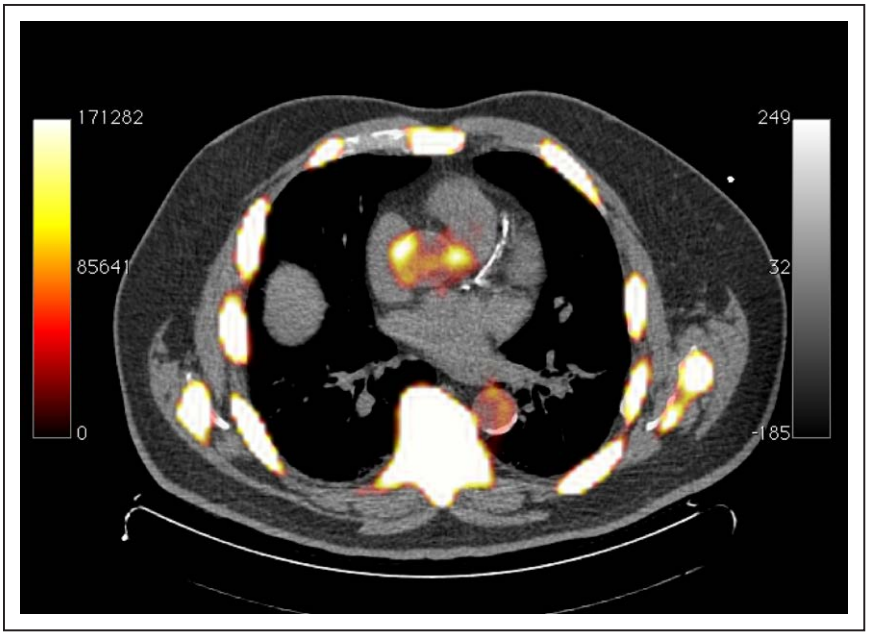

Figure 4. Fused positron emission tomography/computed tomography image showing 2 areas of avid ^{18}F-sodium fluoride uptake in the aortic root where there is no visible calcium and no uptake in the calcified left main and left anterior descending coronary artery.

significance of NaF imaging although substantial technological advancements may be necessary before the implementation of this screening modality.

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Disclosures

None.

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Highlights

- ^{18}F-sodium fluoride has been shown to accumulate in culprit lesions of patients with acute coronary syndromes and in areas of growing hydroxyapatite.
- We tested whether ^{18}F-sodium fluoride detects metabolically active atherosclerotic plaques in ambulatory patients with diabetes mellitus.
- In 88 well-controlled patients with diabetes mellitus, asymptomatic for cardiovascular disease, the prevalence of coronary artery plaques showing high ^{18}F-sodium fluoride uptake was 15%.
- The clinical significance of this finding is unknown.
- Contrary to expectations, the low prevalence of disease may indicate that asymptomatic ambulatory patients with diabetes mellitus are not at high risk of coronary events.