

## Original Article

# Association between atherosclerotic cardiovascular disease risk score estimated by pooled cohort equation and coronary plaque burden as assessed by NaF-PET/CT

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**Abstract:** Pooled Cohort Equations (PCE) combines metabolic and non-metabolic parameters to predict the 10-year risk of atherosclerotic cardiovascular disease (ASCVD). Therefore, we hypothesize that ASCVD risk score is correlated to global cardiac microcalcification, as assessed by <sup>18</sup>F-sodium fluoride-positron emission tomography/computed tomography (NaF-PET/CT). Sixty-one individuals (53.4±8.9 years, 32 females, 100% Caucasian) without known ASCVD underwent NaF-PET/CT imaging. Global cardiac average SUVmean (aSUVmean), also known as the Alavi-Carlson Calcification Score, was calculated across manually defined regions of interest on each axial slice for each individual. The 10-year ASCVD risk score was determined for each individual using the PCE as per ACC/AHA guidelines, and then individuals were categorized into low-, borderline-, intermediate-, and high-risk groups based on their score. Linear regression analysis was applied to compare each individual's ASCVD score and aSUVmean. Global cardiac aSUVmean stratified by groups estimated by 10-year ASCVD risk score were 0.67±0.09 for low risk (n=32), 0.70±0.11 for borderline risk (n=10), 0.72±0.10 for intermediate risk (n=17), and 0.78±0.10 for high risk (n=2). ASCVD risk score was significantly correlated to aSUVmean (r=0.27, P=0.03). This is among the first studies to compare ASCVD risk scores to cardiac plaque burden as assessed by NaF-PET/CT. Large, prospective studies are needed to further investigate the potential of NaF uptake in ASCVD.

**Keywords:** PET/CT, cardiovascular disease, NaF, atherosclerosis, coronary arteries

## Introduction

Atherosclerotic cardiovascular disease (ASCVD) is characterized by the buildup of lipid-derived plaques within the arterial walls, as seen in coronary heart disease, cerebrovascular disease, peripheral artery disease, and aortic atherosclerotic disease [1]. It is caused by the accumulation of oxidized cholesterol within low-density lipoproteins in the vasculature, which leads to inflammation, the formation of a fibrous cap, and plaque deposition within the vessel wall [2]. Globally, ASCVD represents an enormous source of both mortality

and morbidity, particularly in low-resource populations and developing countries, and annual healthcare costs related to these disorders are estimated to approach \$1.1 trillion by 2035 [3-5]. Therefore, a more sophisticated understanding of these diseases must be established to identify, treat, and prevent ASCVD.

To better assess and inform clinical diagnosis surrounding ASCVD, the American College of Cardiology and American Heart Association (ACC/AHA) have developed a scoring system named the ASCVD risk score. Taking a subject's age, sex, race, systolic blood pressure,

total cholesterol, high-density lipoprotein level, antihypertensive therapy status, smoking history, and diabetes mellitus status, the Pooled Cohort Equations (PCE) yield a composite score to predict future probability of adverse ASCVD events. The initial equations in 2013 showed promise and were leveraged in treatment option determinations including statin therapy [6]. Further research led the ACC/AHA to revisit guidelines and create yearly updates, most notably in 2018, regarding score thresholds [7]. Now, the ASCVD score is commonly used clinically ahead of older risk scores (e.g. Framingham Risk Score) to examine topics from drug mechanisms to healthcare utilization [8-10].

Though the ACC/AHA continues to update guidelines to predict ASCVD risk, it is equally important to detect and diagnose arterial calcification early; this is where positron emission tomography (PET) proves valuable. Structural imaging-based scoring, such as computed tomography (CT) calcium score, has been revered as the gold standard, but recent studies demonstrate that molecular imaging modalities better highlight microscopic disease and progression [11]. For years,  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) was used to investigate the local and systemic inflammation secondary to atherosclerosis and coronary heart disease [12, 13]. FDG, a glucose analog, is taken up by metabolically active cells for energy use [14]. Though this is beneficial in inflammatory pathologies, multiple studies have demonstrated that  $^{18}\text{F}$ -sodium fluoride (NaF) is a more sensitive and specific tracer to monitor atherosclerotic microcalcifications [15-17].

There have yet to be any studies that have associated coronary microcalcifications as measured by NaF-PET/CT to clinical ASCVD risk scores determined by the PCE. Therefore, in the present exhibit, we aimed 1) to demonstrate the feasibility of global coronary NaF quantification and 2) to associate these values with ASCVD risk score to demonstrate their clinical utility.

### Methods

#### *Subject selection*

This study included 61 subjects from the prospective Cardiovascular Molecular Calcification Assessed by  $^{18}\text{F}$ -NaF-PET/CT (CAMONA) protocol. We excluded patients in the CAMONA trial with known ASCVD, as well as those under the

age of 40 as ASCVD score cannot be calculated for younger cohorts. The CAMONA study was approved by the Danish National Committee on Biomedical Research Ethics, registered at ClinicalTrials.gov (NCT01274749) and conducted from 2012 to 2016 in accordance with the Declaration of Helsinki [18]. All subjects gave written informed consent prior to the study. All subjects underwent a standard physical examination and blood testing and completed questionnaires about smoking history, alcohol consumption, and physical activity level. Subjects were subsequently divided into four groups as defined by 10-year ASCVD risk score per AHA/ACC PCE guidelines: low-risk (<5%; n=32), borderline-risk (5-7.4%; n=10), intermediate-risk (7.5-19.9%; n=17), and high-risk ( $\geq 20\%$ ; n=2).

#### *Image acquisition*

All subjects underwent whole-body NaF-PET/CT imaging on hybrid PET/CT scanners with a comparable spatial resolution (GE Discovery RX, STE, and 690/710 imaging systems) 90 minutes after the administration of 2.2 MBq/kg dose of NaF intravenously. Low-dose CT imaging (140 kV, 30-110 mA, noise index 25, 0.8 seconds/rotation, slice thickness 3.75) was performed for attenuation correction and structural correlation, and PET scans were corrected for scattering, attenuation, and dead time.

#### *Image analysis*

OsiriX MD software v.10.0.2 (DICOM viewer and image-analysis program, Pixmeo SARL; Bernex, Switzerland) was used to analyze the NaF-PET/CT scans. On the fused PET/CT images, CT-based regions of interest (ROIs) were hand-drawn for the global assessment of the heart while excluding the cardiac valves, aortic wall, and skeletal structures (**Figure 1**). This methodology to measure the global coronary activity has been previously established by several studies in the literature and has been shown to demonstrate low variability [19-22]. Mean standardized uptake value (SUVmean) and ROI volume were determined for each trans-axial slice. NaF uptake within each slice was calculated by multiplying slice SUVmean by the corresponding slice ROI volume. Utilizing the Alavi-Carlson Calcification Score methodology, NaF uptake was summed across all the slices and then divided by the total ROI volume to generate global cardiac average SUVmean (aSUVmean) [22-24]. aSUVmean was

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**Figure 1.** Axial view of a NaF-PET slice (A), and a fused NaF-PET/CT slice without (B) and with the cardiac region of interest (C) in a 59-year-old individual. The manually-delineated regions of interest in all cardiac slices determined the global coronary artery NaF uptake and did not include uptake from the aortic valve, skeletal structures, and aortic wall.

**Table 1.** Subject demographics

	Total (N=61)
Age (years)	53.4±8.9
Systolic blood pressure (mmHg)	125.1±14.9
Diastolic blood pressure (mmHg)	72.7±9.4
Mean arterial pressure (mmHg)	90.2±10.7
Low density lipoprotein (mg/dL)	108.2±29.8
Total cholesterol (mg/dL)	179.4±32.0
Triglycerides (mg/dL)	73.0±23.9
High density lipoprotein (mg/dL)	56.4±14.0
Plasma glucose (mg/dL)	97.7±8.7
HbA1c (%)	5.1±0.3
CRP (mg/L)	1.3±0.6

Values are mean ± SD, HbA1c = Glycated hemoglobin.

calculated across the entire heart for each individual and used for statistical analysis. The association between ASCVD risk score and aSUVmean was evaluated. The aSUVmean and the ASCVD risk score were compared by linear regression, and scatter plots were generated for visualization of data, including a linear fit to the data and a respective 95% confidence band. A  $p$ -value  $<0.05$  was chosen as being statistically significant. We used Statistical software packages SPSS (Version 25.0, IBM), R (R Core Team 2020), and STATA/MP 16.1 (StataCorp, College Station, Texas 77845, USA) for the statistical analysis and generating figures.

### Results

Sixty-one subjects (53.4±8.9 years, 32 females, 100% Caucasian) were included in this analysis. Cardiovascular laboratory values for this cohort are summarized in **Table 1**.

Global cardiac aSUVmean was observed to be greater in subgroups with higher 10-year risk for ASCVD. Specifically, NaF uptake was  $0.67 \pm 0.09$  in low-risk subjects ( $n=32$ ),  $0.70 \pm 0.11$  for borderline-risk subjects ( $n=10$ ),  $0.72 \pm 0.10$  for intermediate-risk subjects ( $n=17$ ), and  $0.78 \pm 0.10$  for high-risk subjects ( $n=2$ ). In addition, males demonstrated significantly higher aSUVmean compared to females ( $\text{mean}_{\text{male}}=0.72$ ,  $\text{mean}_{\text{female}}=0.67$ ,  $P=0.03$ ).

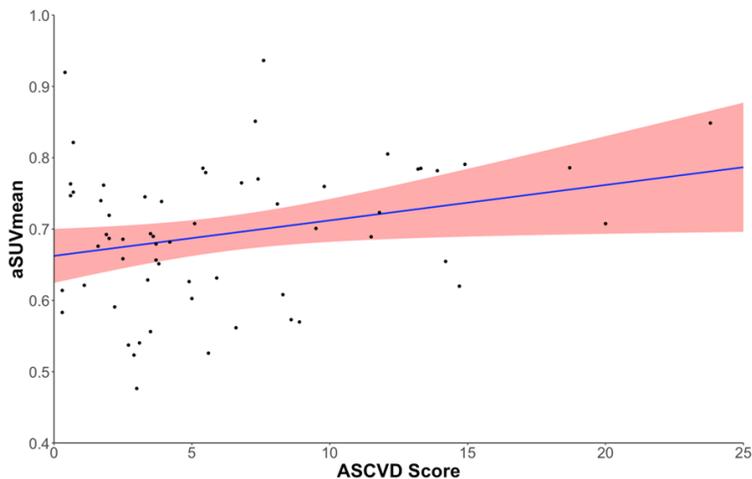
Subsequently, linear regression analysis was utilized to associate aSUVmean with ASCVD risk score. Global NaF uptake was significantly, positively correlated to 10-year risk for ASCVD ( $r=0.27$ ,  $P=0.03$ ) (**Figure 2**), though no such correlation was observed when stratified by gender.

### Discussion

ASCVD risk score has been increasingly utilized by physicians to estimate patient risk and guide treatment options. This study is among the first to delineate an association between ASCVD risk score, a clinically established calculator for morbidity and mortality, and plaque burden as detected by NaF-PET/CT. By demonstrating the ability of this non-invasive modality to localize atherosclerotic lesions, these results may inform management of at-risk patients before the onset of adverse cardiovascular events.

Previous studies have demonstrated the sensitivity and specificity of NaF-PET/CT in the detection and quantification of intraluminal plaques. Li *et al.* compared NaF-PET/CT to coronary intravascular ultrasound, and they determined that NaF-PET/CT can be used as an effective method to evaluate the global extent

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**Figure 2.** Linear regression and 95% confidence interval between ASCVD risk score and calculated aSUVmean ( $r=0.27$ ,  $P=0.03$ ).

of atherosclerotic plaques and plaque burden [25]. In addition, Dweck *et al.* assessed valvular calcification in patients presenting with aortic stenosis, and they found that, while both FDG and NaF uptakes were significantly increased with the presence of calcification and associated inflammation, NaF uptake was a more sensitive and specific indicator of the severity of the valvular disease [26, 27]. Taken together, these findings demonstrate the clinical significance of NaF-PET/CT as a more sensitive and specific method of plaque detection than traditional visualization techniques.

In our study, we correlated numeric NaF uptake to national ASCVD guidelines. Previous studies have also examined molecular imaging in high-risk populations. Blomberg *et al.* determined that coronary NaF uptake, but not FDG uptake, was significantly associated with age and cardiovascular disease (CVD) risk factors, as estimated by Framingham risk score [28]. Arani and coworkers came to similar conclusions using the abdominal aortas of subjects from the CAMONA study, again demonstrating the superiority of NaF to FDG as a tracer for molecular calcifications and the identification of age-related risk factors for CVD [29]. Furthermore, Castro *et al.* concluded that NaF uptake in the common carotid arteries was significantly positively associated with Framingham cardiovascular risk factors, such as age, hypercholesterolemia, hypertension, and body mass index [30]. Data from the same group also established significant corre-

lations between NaF average SUVmean and white blood cell count, hemoglobin A1c, and homocysteine, all of which are biomarkers for plaque vulnerability [31]. Payday *et al.* determined that active calcification in the thoracic aorta measured by NaF-PET/CT is correlated with age [32]. In addition, they further demonstrated that NaF uptake is higher in subjects with cardiovascular risk factors. Interestingly, de Oliveira-Santos *et al.* found that, although the degree of NaF uptake in plaques was associated with an increased burden of cardiovascular risk factors,

there was no correlation between NaF uptake and calcium score [33]. Recently, Sorci *et al.* utilized NaF-PET/CT to evaluate whole-heart arterial calcification in 36 patients from the CAMONA study [20]. They found that, compared to calcium score and Framingham risk score, NaF-PET/CT SUV values were different between patients and controls, and they were also indicative of disease state, thus serving a more beneficial role in the assessment of coronary artery disease. Kwiecinski *et al.* similarly investigated the utility of NaF-PET/CT as a predictive indicator of myocardial infarction in patients with coronary artery disease. They found that increased NaF uptake occurred only in patients who experienced fatal or non-fatal myocardial infarction [34]. Taken together, these data demonstrate that NaF-PET/CT is correlated with known cardiovascular risk factors and risk scores, pointing toward a clinical utility for nuclear imaging in these populations.

A major strength of the present study is the standardization of methodology, including scanner resolution, radiotracer dosage, and acquisition protocol, among subjects. Furthermore, our methodology utilizes global PET analysis by global cardiac aSUVmean. Maximal standardized uptake value (SUVmax) is an oversimplified measurement of plaque burden, as it can be manipulated by noise and scanner variability [23]. In contrast, our assessment of ASCVD risk by aSUVmean is readily reproducible and offers a sensitive and speci-

fic measurement of coronary plaque burden [35, 36]. This will enable physicians to more easily and consistently apply these data in a clinical setting.

There were several limitations to this study. This was a retrospective study of a relatively small subject cohort of entirely Caucasian individuals; although we can attribute the results of our study to factors other than race, our results may not be generalizable to non-Caucasian demographics. Additionally, the stepwise increase seems to sustain the hypothesis of a positive relationship. Another limitation is that the study design was cross-sectional, and thus the understanding of temporal associations and subsequent morbidity and mortality outcomes in our cohort cannot be properly assessed. Future aims should be larger tailored prospective studies to strengthen the results presented here and validate the relationship between these factors.

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### Disclosure of conflict of interest

None.

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