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Original Article

Utilization of NaF-PET/CT in assessing global cardiovascular calcification using $CHADS_2$ and $CHADS_2$-VASc scoring systems in high risk individuals for cardiovascular disease

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Abstract: $CHADS_2$ and CHA_2DS_2-VASc scores are used to estimate the risk of strokes in patients with atrial fibrillation. We sought to determine the global quantification of cardiovascular molecular calcification in high risk individuals by NaF-PET/CT and compare it with $CHADS_2$ and CHA_2DS_2-VASc scores. We identified 40 high risk individuals for cardiovascular disease from the Cardiovascular Molecular Calcification Assessed by ^{18}F-NaF PET CT (CAMONA) trial and calculated $CHADS_2$ and $CHADS_2$-VASc scores for each. Ninety minutes after NaF injection (2.2 Mbq/kg), PET/CT imaging was performed. CT imaging was done for attenuation correction and anatomic correlation. The global cardiac uptake was calculated from regions of interest manually drawn on axial PET/CT images made in OsirixMD. Global cardiac average SUVmean (aSUVmean) values were calculated, and linear regression analysis was employed for statistical purposes. Subjects had mean age of 55 ± 11.9 SD years, (Range: 23-73 years), female 55%. The sample consisted of subjects with a mean aSUVmax of 2.9 ± 1.4, aSUVmean was 0.8 ± 0.2, $CHADS_2$ 0.9 ± 0.6 (Range: 0-3), CHA_2DS_2-VASc 1.8 ± 1.3 (Range: 0-5). Based on the linear regression models, we found a direct correlation between global cardiac aSUVmean and $CHADS_2$ score ($r=0.58$, $P\leq0.0001$) and also between global cardiac aSUVmean and CHA_2DS_2-VASc ($r=0.37$, $P=0.01$). Based on the results of our study we conclude that patients with a higher $CHADS_2$ and CHA_2DS_2-VASc scores had a higher atherosclerotic burden and could be at greater risk of cardiovascular events. These scoring systems can help with risk stratification for predicting future adverse atherosclerotic events.

Keywords: $CHADS_2$, CHA_2DS_2-VASc, NaF, PET, CT, cardiovascular imaging

Introduction

$CHADS_2$ (scored as 1 point each for congestive heart failure, hypertension, diabetes mellitus, age ≥75 years, and 2 points for past stroke/transient ischemic attack) and CHA_2DS_2-VASc (scored as 1 point each for congestive heart failure, hypertension, diabetes mellitus, vascular disease, age 65 to 75 years, or female sex, and 2 points each for age ≥75 years or past stroke/transient ischemic attack) scores have been previously used to predict risk of systemic thromboembolism in patients with non-valvular atrial fibrillation [1-3]. Patients with atrial fibrillation who had a higher $CHADS_2$ and CHA_2DS_2-VASc score were associated with an increased risk of strokes, and atherosclerosis. There is data suggestive that these scoring systems are predictive of severity of atherosclerotic disease and major cardiovascular events regardless of arrhythmic status [4-6].

The mechanisms behind vascular calcification are complex and not well understood. However,

microcalcifications are mainly composed of hydroxyapatite, which are seen in the fibrous caps of the plaques. ^{18}F-sodium fluoride (NaF) incorporates into these hydroxyapatite crystals, allowing NaF to be used with positron emission tomographic (PET) for microcalcification detection [7]. There has been an increasing trend to utilize this imaging modality for assessing cardiovascular disease and calcification [8-10]. Previous evidence has shown promise using NaF uptake with PET/computed tomography (CT) as a new non-invasive molecular imaging technique to identify high risk plaques [11, 12]. NaF activity can localise to regions of plaque with high risk features such as microcalcification, and a large necrotic core; these rupture prone areas are also known as thin-cap fibroatheromas (TCFA) (<65 μm thick) [13]. Thus, these regions often have high uptake and are sensitively visible on PET/CT scans.

Currently, no prior studies to our knowledge have attempted to directly correlate $CHADS_2$ and CHA_2DS_2-VASc scores with NaF uptake in atherosclerotic plaque. We believe this is an important correlation to determine as $CHADS_2$ and CHA_2DS_2-VASc scores can be leveraged for early predictions of cardiovascular disease. Thus, the aim of this study is two-fold: to quantify global cardiac microcalcification in patients at risk for cardiovascular disease as assessed by NaF uptake on PET/CT and correlate this uptake with $CHADS_2$ and CHA_2DS_2-VASc scores. We hypothesize that global cardiac microcalcification will correlate positively with $CHADS_2$ and CHA_2DS_2-VASc scores.

Methods

Subjects

We identified 40 patients at-risk of cardiovascular disease from the prospective study known as "Cardiovascular Molecular Calcification Assessed by ^{18}F-NaF PET/CT (CAMONA)" in Odense, Denmark. The CAMONA study was approved by the Danish National Committee on Biomedical Research Ethics as well as registered at ClinicalTrials.gov (NCT01724749). The study was undertaken in concordance with the Declaration of Helsinki and all subjects provided written informed consent. Subjects in this population were checked for the presence of malignancy, immunodeficiency syndrome, autoimmune disease, pregnancy, sarcoidosis, amyloidosis, endocarditis, symptoms suggestive of cardiovascular disease (CVD) such as syncope, chest pain, and shortness of breath, as well as prescription medications, to be excluded from the study.

As we planned to determine the role of ^{18}F-NaF uptake on PET/CT, we excluded subjects who did not have both the standardized PET scan and attenuated CT scan. Standard uptake value is defined from the following equation: radioactive concentration in tissue/(injected dose/subject body weight). And thus, if a subject's weight could not be considered, the subject was excluded. After these exclusions were made, we had a total of 40 subjects with a mean age of 55 years, ranging from 23-73 years ± 11.9 SD, majority were female 55%.

Quantitative image analysis

All subjects underwent ^{18}F-NaF-PET/CT imaging with an established and uniform protocol (GE Discovery STE, VCT, RX, and 690/710). Patients were made to observe an overnight fast of 8 hours and a blood glucose measurement ensuring a concentration below 8 mmol/L. ^{18}F-NaF-PET/CT imaging was performed 90 minutes following the intravenous injection of 2.2 MBq of ^{18}F-NaF per kilogram of body weight. These images were produced using one of several PET/CT systems (GE Discovery STE, VCT, RX, and 690/710). PET images were also corrected for attenuation, scatter, scanner dead time, and random coincidences. Low-dose CT imaging (140 kV, 30-110 mA, noise index 25, 0.8 seconds per rotation, slice thickness 3.75 mm) was then performed for attenuation correction and anatomic referencing with PET images.

Quantification of vascular ^{18}F-NaF uptake was performed by a trained physician by manually placing a free-hand region of interest (ROI) around the cardiac silhouette on each slice of the axially oriented PET/CT images using a DICOM viewer (Osirix MD Software; Pixmeo SARL, Bernex, Switzerland) (**Figure 1**). The methodology used to place ROIs has been established in numerous other studies and has low variability [14-17]. The ROI did not include any parts of the skeleton, cardiac valves, or aortic wall. For every ROI, representing the volume of one cardiac slice, the NaF activity was

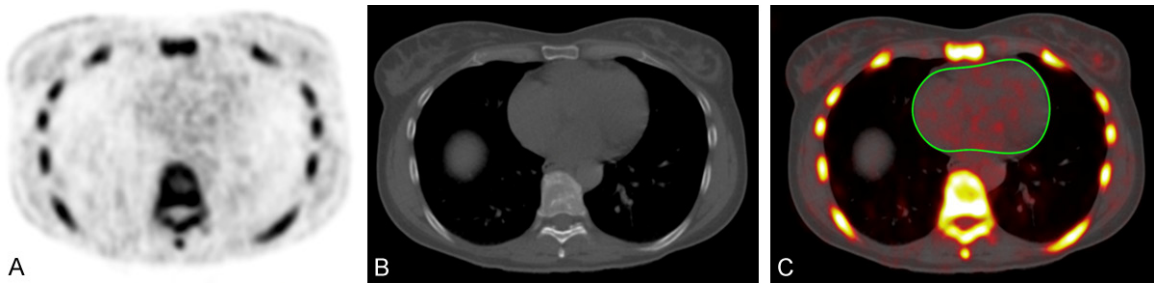

Figure 1. Axial view NaF-PET (A), CT (B), and fused NaF-PET/CT (C) images with region of interest in an at-risk subject (C). The manually-delineated region of interest determined the global coronary artery NaF uptake and did not include uptake from the aortic valve, skeletal structures, and aortic wall.

Table 1. Subjects *CHA_2DS_2-VASc* and *$CHADS_2$* score demographics

Clinical Factors	CHA_2DS_2-VASc	$CHADS_2$
Congestive Heart Failure	0	0
Hypertension	24	24
Age		
<65 years	30	-
65-74 years	9	-
≥75 years	1	1
Diabetes Mellitus	0	0
Stroke/TIA/Thromboembolism	2	2
Vascular Disease (Prior MI, PAD)	8	8
Female	22	-

TIA: transient ischemic stroke; MI: myocardial infarction; PAD: peripheral artery disease.

Table 2. Other demographic variables

Variables	Percentage
Atrial Fibrillation	6 (15%)
History of Stroke	2 (5%)
History of PAD	5 (12.5%)
History of CAD	3 (7.5%)
History of Hypercholesterolemia	11 (27.5%)
Smoker	15 (37.5%)
Alcohol Use	37 (92.5%)
Average Systolic Blood Pressure (mm Hg)	129 ± 17.5
Average Diastolic Blood Pressure (mm Hg)	79 ± 7.5
Total Cholesterol (mmol/L)	5.3 ± 0.9
Low Density Lipoprotein (mmol/L)	3.4 ± 0.8
Triglycerides (mmol/L)	1.2 ± 0.8
Aspirin Usage	8 (20%)
Lipid Lowering Medication	12 (30%)
HbA1c (mmol/L)	34.7 ± 3.1
Plasma Glucose (mmol/L)	5.6 ± 0.7

PAD: peripheral artery disease; CAD: coronary artery disease.

determined as the mean standardize uptake value (SUVmean). Then, these values were added and divided by the sum of the ROI-defined slice volumes to yield a global cardiac average SUVmean (aSUVmean).

Statistical analysis

The association between CHA_2DS_2-VASc, $CHADS_2$ and the aSUVmean of the whole heart was evaluated. The global cardiac aSUVmean between CHA_2DS_2-VASc and $CHADS_2$ were compared using linear regressions. A p value <0.05 was chosen as being statistically significant. We used Statistical software packages SPSS (Version 25.0, IBM) and STATA/MP 16.1 (StataCorp, College Station, Texas 77845 USA) for the statistical analysis and generating figures.

Results

In this study, we included a total of 40 subjects with a mean age of 55 years, ranging from 23-73 years ± 11.9 SD, majority were female 55% (**Table 1**). The sample consisted of subjects with a mean aSUVmax of 2.9 ± 1.4, aSUVmean was 0.8 ± 0.2, $CHADS_2$ 0.9 ± 0.6 (Range: 0-3), CHA_2DS_2-VASc 1.8 ± 1.3 (Range: 0-5), Systolic Blood pressure 129 ± 17.5, diastolic blood pressure 79 ± 7.5. Among these subjects, rates of co-morbidities were: Atrial fibrillation 6 (15%), Stroke 2 (5%), Peripheral artery disease 5 (12.5%), Coronary artery disease 3 (7.5%), hypertension 24 (60%), Hypercholesterolemia 11 (27.5%), Smoker 15 (37.5%), Alcohol use 37 (92.5%) (**Tables 2**, **3**). Sample also included 8 (20%) with Aspirin use and 12 (30%) on lipid lowering medication. Our study popula-

Table 3. Subjects *CHA_2DS_2-VASc* and *$CHADS_2$* scores

Score	CHA_2DS_2-VASc	$CHADS_2$
0	6	9
1	11	28
2	12	2
3	6	1
4	4	0
5	1	0
6	0	0
N=40		

tion did not have a history of diabetes or heart failure. The linear regression model had a positive correlation between global cardiac aSUVmean and $CHADS_2$ score (r=0.58, P≤0.0001; **Figure 2A**). The linear regression between global cardiac aSUVmean and CHA_2DS_2-VASc was also found to be significant (r=0.37, P=0.02; **Figure 2B**).

Discussion

In this study, we evaluated global cardiac microcalcification in patients at risk for cardiovascular disease as assessed by NaF uptake on PET/CT against $CHADS_2$ and CHA_2DS_2-VASc scores. We found that the linear regression model had a positive correlation between global cardiac aSUVmean and $CHADS_2$ and CHA_2DS_2-VASc score; moreover, $CHADS_2$ had a higher linear correlation compared to CHA_2DS_2-VASc scores in assessing global cardiac NaF uptake on PET/CT, indicating that patients with a higher $CHADS_2$ and CHA_2DS_2-VASc score are associated with a greater atherosclerotic burden.

$CHADS_2$ and CHA_2DS_2-VASc risk scores are simple, easy to use and well validated tools which have been utilized for risk stratification in stroke prevention and guide anticoagulation among patients with atrial fibrillation [2-4]. American College of Cardiology/American Heart Association/European Society of Cardiology guidelines recommend initiating anti-coagulation for patients with atrial fibrillation with a $CHADS_2$ score or CHA_2DS_2-VASc of ≥1. It is recommended to apply CHA_2DS_2-VASc score in patients who have a $CHADS_2$ score of 0 for further risk stratification as $CHADS_2$ does not include female gender, vascular disease, and age 65-74. Due to these limitations CHA_2DS_2-VASc scoring system has been utilized more frequently as it provides more robust information on the risk factors which could predict atherosclerotic events. There is growing awareness and evidence for its use in risk stratification of patients with coronary artery disease (CAD) without Atrial fibrillation. If the non-invasive imaging modality using NaF PET/CT can help identify and differentiate high risk plaques it would be a great tool in the future for prevention and treatment of CAD.

These findings are consistent with other studies which have showed similar results even in patients without Atrial fibrillation [4, 18, 19]. Prior data has suggested that these scoring systems have a role in predicting long term outcomes in patients with CAD and Acute coronary syndrome. In regard to Tasolar et al., CHA_2DS_2-VASc-HS score correlated positively with the severity and complexity of CAD [5]. Other similar studies have shown that $CHADS_2$ score predicted long-term mortality in CAD [2, 18-21]. However, it should be noted that each variable in these scoring systems can independently be a risk factor in patients with coronary artery disease and stroke. Atherosclerosis is considered as a disease of aging and additional risk factors such diabetes, hypertension, smoking, hyperlipemia can accelerate the process of atherosclerosis. Diabetes and hypertension can cause atherosclerosis due to activation of advanced glycation end-products and reactive oxygen species [22, 23]. Other possible reasons for elevated risk of cardiovascular events could be related to endothelial dysfunction, hypercoagulability in patients with diabetes, hypertension, heart failure and older age. In our study, the majority of the subjects were <65 years, females, non-diabetic and had a history of hypertension.

Atherosclerotic calcification occurs due to cellular necrosis, inflammation, and cholesterol deposition at sites of atherosclerotic plaques [24]. Prior studies have shown that NaF has an important role in detecting active unstable atherosclerosis by being able to differentiate between macro and microcalcifications [7, 11, 13, 25, 26]. However, Alavi et al have described the difficulty in visualizing atherosclerotic plaques using PET due to smaller size of vessels and poor spatial resolution due to arterial wall motion related to cardiac cycle [16, 27, 28]. The same group sought to detect and measure global cardiac calcification to measure coro-

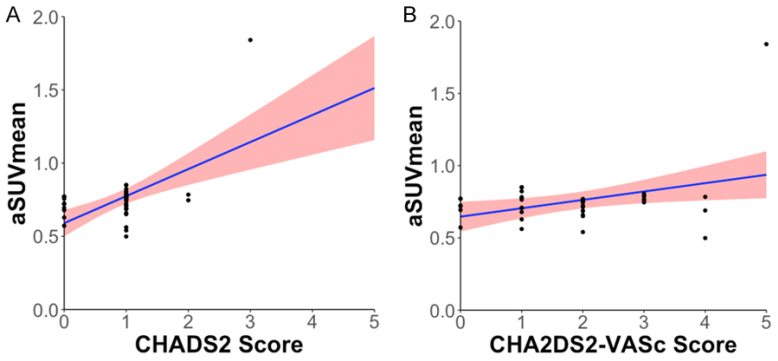

Figure 2. Correlation of global cardiac aSUVmean against (A) $CHADS_2$ score (P≤0.0001) and (B) CHA_2DS_2-VASc score (P=0.02). Linear regression line listed ± 95% confidence interval.

nary atherosclerosis so as to overcome these limitations [29]. Multiple imaging modalities (such as fluoroscopy, echocardiography, intravascular ultrasound, electron beam computed tomography, coronary artery calcium, cardiac CT) can identify vascular calcification but can lack specificity [30]. Stress testing and coronary angiography may pick up obstructive plaques but can miss non-obstructive high-risk plaques which could cause myocardial infarction [31]. These high-risk atherosclerotic rupture prone plaques can be picked up by NaF. Other tracers such as fluorodeoxyglucose have been studied to identify coronary atherosclerosis and have proven to be effective in identifying vascular inflammation in the aorta and carotid arteries, but its role to detect atherosclerosis of coronary artery vasculature is limited because of its high myocardial uptake [32-34]. Macrocalcifications can be identified with coronary artery calcium and cardiac CT but they do not play a significant role in identifying high risk plaques which could lead to acute thrombosis [30, 35, 36]. Other invasive modalities such as optical coherence tomography, gray-scale intravascular ultrasound have been investigated to detect TCFA but the results of the study were not optimal [37]. Amount of calcium in high risk plaques vary and have resembled other non-high risk plaque types determined by histopathology. Therefore, IVUS demonstrating spotty calcification might not be a valid marker for identifying high risk plaques and also because of its invasive nature it cannot be used a screening test.

Despite the correlations drawn, there are important limitations to consider. Our study sample size is relatively small and as such, future studies should study a larger cohort sample size. Furthermore, our study design was a cross sectional analysis and therefore a longitudinal study assessing temporal associations and outcomes would be useful. Further studies need to be done to establish if patients who had plaques with high risk features subsequently developed major adverse cardiac or cerebrovascular events. Our study did not have any patients with a history of diabetes or heart failure, two factors that can severely affect outcomes. Lastly, as we aimed to assess atherosclerosis at a molecular level, histopathological samples would have been helpful to confirm our NaF PET/CT findings.

Conclusion

In conclusion, $CHADS_2$ and CHA_2DS_2-VASc risk scores are simple tools which can be useful predictors of atherosclerotic burden and can help with risk stratification for predicting future adverse atherosclerotic events. Based on the results of our study we conclude that patients with a higher score has a higher atherosclerotic burden and could be at greater risk of cardiovascular events. It is important to optimize these risk factors by aggressive management policies. Further validation studies are needed to comment on their association and the utility of NaF as a novel marker in assessing atherosclerotic burden.

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Disclosure of conflict of interest

None.

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