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# Carotid FDG Uptake Improves Prediction of Future Cardiovascular Events in Asymptomatic Individuals

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## ABSTRACT

**OBJECTIVES** This study sought to investigate the role of carotid fluoro-2-deoxyglucose (FDG) uptake as an independent prognostic indicator and to determine whether its addition improves risk prediction beyond the Framingham risk score (FRS) and carotid intima-media thickness (CIMT).

**BACKGROUND** The prognostic value of carotid FDG uptake independent of and incremental to traditional cardiovascular risk factors and CIMT in asymptomatic individuals has not been evaluated.

**METHODS** We measured carotid FDG uptake and CIMT in 1,089 asymptomatic adults (51.8 ± 6.3 years of age, 94.3% males) who underwent positron emission tomography/computed tomography imaging and examined the prognostic value of carotid FDG uptake compared with traditional risk factors and CIMT.

**RESULTS** Cardiocerebrovascular events occurred in 19 participants (1.74%) during an average follow-up of 4.2 years (range 1.0 to 5.5 years). Multivariable Cox proportional hazards analyses revealed that high carotid FDG uptake (hazard ratio: 2.98; 95% confidence interval: 1.17 to 7.62; $p = 0.022$) and high CIMT (hazard ratio: 2.82; 95% confidence interval: 1.13 to 7.03; $p = 0.026$) were independent predictors of events. Comparison of predictive power demonstrated that adding carotid FDG uptake, but not CIMT, to the FRS significantly increased the time-dependent area under the receiver-operating characteristic curve from 0.60 to 0.73 ($p = 0.04$). Furthermore, improvement approaching significance was achieved by adding carotid FDG uptake to the FRS plus CIMT, which increased the area under the receiver-operating characteristic curve from 0.65 to 0.75 ($p = 0.07$). Net reclassification for event prediction was similarly improved by addition of carotid FDG uptake to the FRS (net reclassification index, 40.1%; $p = 0.06$), as well as the FRS plus CIMT (net reclassification index, 32.9%; $p = 0.07$).

**CONCLUSIONS** High carotid FDG uptake predicts cardiovascular events independent of traditional risk factors and CIMT in asymptomatic adults and may add to risk stratification beyond the FRS and CIMT. (J Am Coll Cardiol Img 2015;8:949-56) © 2015 by the American College of Cardiology Foundation.

Inflammation plays a key role in atherosclerosis progression and triggers plaque instability (1-3), the major pathophysiology underlying myocardial infarction and stroke (4,5). Accordingly, there is accumulating evidence suggesting the usefulness of inflammatory biomarkers for predicting cardiocerebrovascular events (6-9). For example, serum high-sensitivity C-reactive protein (hsCRP) has been shown to correlate with traditional risk factors (9) and predict cardiovascular risk in apparently healthy adults (6,7) and unstable angina patients (8). Fluorine 18-fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) is a noninvasive imaging study widely used for cancer. Because activated macrophages avidly take up FDG, PET can also detect inflammatory lesions with high sensitivity, with uptake magnitude as an indicator of inflammation severity (10-13). This has led to an increasing interest

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**ABBREVIATIONS AND ACRONYMS**

**AUC** = area under the receiver-operating characteristic curve

**CIMT** = carotid intima-media thickness

**CT** = computed tomography

**FDG** = fluoro-2-deoxyglucose

**FRS** = Framingham risk score

**hsCRP** = high-sensitivity C-reactive protein

**IDI** = integrated discrimination improvement

**M-TBR** = maximal target-to-blood pool ratio

**NRI** = net reclassification index

**PET** = positron emission tomography

**SUV** = standard uptake value

**TFD** = tip of the flow divider

in the use of FDG PET in atherosclerosis, and many studies point to a positive correlation between arterial uptake and traditional cardiac risk factors (14,15). There have been a few recent attempts to evaluate an association between arterial FDG uptake and subject outcome (16–18). However, these studies were limited by a small number of subjects, underlying cancer disease, short follow-up, and failure to compare with traditional risk factors (16,17). In a more recent study, Figueroa et al. (18) examined the prognostic utility of FDG PET in patients without a history of active cancer and compared the findings with traditional risk factors, but assessment of FDG uptake was restricted to large arteries. The precise prognostic value of carotid FDG uptake for future cardiovascular events, therefore, remains to be explored.

In this study, we evaluated a large cohort of asymptomatic adults to investigate the role of carotid FDG uptake as an independent prognostic indicator and to determine whether its addition improves risk prediction beyond the Framingham risk score (FRS) and carotid intima-media thickness (CIMT).

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## METHODS

**SUBJECTS.** The study candidates were 2,329 consecutive participants in a health screening program that included FDG PET/computed tomography (CT) for cancer screening at our institution between January 2009 and November 2009. From this population, 1,226 subjects, who also had carotid ultrasonography measurements of CIMT and had all clinical data necessary for calculation of the FRS, were selected. Among these, 16 subjects were excluded because of pre-existing coronary heart disease (n = 4) and stroke (n = 12); 29 subjects were excluded for lack of PET/CT data (n = 14), inaccessible electronic medical records (n = 1), or carotid uptake obscured by adjacent tissue (n = 14). Additionally, 92 subjects were excluded because of being lost to follow-up (n = 61) or follow-up was <1 year (n = 31). Thus, 1,089 subjects were finally included. None of the subjects had cardiac or neurological symptoms at the time of PET/CT. The institutional review board approved this retrospective cohort study, and the requirement to obtain informed consent was waived.

**MEASUREMENT OF CIMT.** CIMT was measured by experienced radiologists using Vivid (GE Vingmed Ultrasound AS, Horten, Norway) or EKO-7 (Samsung Medison America, Cypress, California) high-resolution B-mode ultrasound system equipped with 7-MHz linear transducers and an automated IMT package, according to a standardized protocol. Briefly, CIMT was measured during the end-diastolic phase between the P and Q waves from the electrocardiogram trace in 3 segments: the common carotid artery from 10 to 20 mm proximal to the tip of the flow divider (TFD), carotid bifurcation from the TFD to 10 mm proximal to the TFD, and the internal carotid artery from the TFD to 10 mm distal to the TFD. The composite CIMT, calculated as the mean of both sides of 3 carotid segments, was used.

**PET/CT IMAGING.** All subjects were instructed to fast for at least 6 h before the PET/CT study, and blood glucose levels were <200 mg/dl at the time of FDG injection. Imaging was performed in the majority of the subjects (n = 1,082) using a GE Healthcare STE scanner (Wauwatosa, Wisconsin), whereas a GE Discovery LS scanner was used in 7 subjects. At 45 min after injection of 370 MBq FDG, CT images were acquired, using an 8-slice (140 KeV, 40 to 120 mA adjusted to body weight; 5-mm section width) or 16-slice helical CT (140 KeV, 30-170 mA with an Auto A mode; 3.75-mm section width). No intravenous or oral contrast materials were used. PET images were then acquired from thigh to head for 4 min per frame in the 2-dimensional mode. Attenuation-corrected PET images (voxel size 4.3 × 4.3 × 3.9 mm) were reconstructed using CT data by an ordered-subset expectation maximization algorithm (28 subsets, 2 iterations).

**PET/CT IMAGE ANALYSIS.** Transaxial FDG PET/CT slices of 4.3-mm (Discovery LS) or 3.3-mm (STE) thickness were analyzed on a Xeleris workstation (GE Healthcare). Circular or ellipsoidal regions of interest were manually placed over the carotid arteries on every other tomographic slice beginning from the merging point with the brachiocephalic trunk or aortic arch up to 4 to 6 slices above the bifurcation site, as previously described (19). The maximal standard uptake values (SUVs) of each arterial segment were averaged for both carotid arteries and then divided by the background SUV to yield the maximal target-to-blood pool ratios (M-TBRs) for each subject.

**DEFINITION OF VARIABLES.** Subjects over the 75th percentile of M-TBR were regarded as having elevated carotid FDG uptake, classified as inflammation of the carotid artery. Subjects over the 75th percentile of CIMT were classified as having elevated CIMT. The FRS of subjects was obtained by using a calculator of the openly accessible website (20).

Abnormal clinical and laboratory findings were based on the criteria for metabolic syndrome modified for Asians (21,22). Cardiocerebrovascular events included a myocardial infarction, any coronary intervention, angina requiring an emergency department visit, an ischemic stroke, or transient cerebral ischemic attack.

**STATISTICAL ANALYSIS.** Comparison of the difference between 2 groups was performed using Student *t* test for continuous variables and chi-square test for dichotomous variables. Univariate and multivariate analyses using Cox proportional hazards regression models were conducted to identify the prognostic indicator of cardiocerebrovascular events. Demographic characteristics, clinical variables, the FRS, CIMT, and carotid inflammation were assessed.

Predictive performance of prognostic models was measured by the time-dependent area under the receiver-operating characteristic curve (AUC) (23). Bootstrapping was performed to obtain confidence intervals for the difference in adjusted AUC between indicators and to adjust for over-optimism that can occur when the fit of the model is tested using the same data in which it was described (24). Continuous net reclassification indexes (NRIs) were estimated to examine the net effect of adding a marker to the risk prediction scheme. Integrated discrimination improvement (IDI), the difference in an $R^2$-like statistic between 2 models, was also estimated. AUC, NRI, and IDI were calculated for 4-year follow-up, and confidence intervals were obtained by bootstrapping (24).

SPSS for Windows version 16.0 (SPSS Inc., Chicago, Illinois) was used for the Student *t* test, chi-square test, and Cox proportional hazards regression models. The "timeROC" package (25), written using the open-source statistical software R (R Foundation, Vienna, Austria), was used for time-dependent receiver-operating characteristic curve estimation, and the AUC and "survIDINRI" package (26) was used for IDI and NRI estimations. Two-sided p values of <0.05 were considered significant.

## RESULTS

**CHARACTERISTICS OF STUDY SUBJECTS.** The study population had a mean age of 51.8 ± 6.3 years (range 33 to 97 years) and a high male preponderance that reached 94.3%. The mean FRS was 12.2 ± 8.6% (median 9.8%; interquartile range: 6.5% to 14.7%). When we compared this study population (subjects who had CIMT measurements; n = 1,089) with subjects who did not have CIMT measurements (n = 1,103), a higher male preponderance and younger age was noted for the former group. Importantly, however, there was no difference in the FRS between the 2 groups, and this remained true when only male subjects were analyzed (data not shown).

On average, participants had a carotid M-TBR of 1.59 ± 0.15 (right, 1.65 ± 0.16; left, 1.56 ± 0.15) and CIMT of 0.65 ± 0.14 mm (right, 0.65 ± 0.18 mm; left, 0.66 ± 0.15 mm). Subjects with M-TBR over the 75th percentile (right ≥1.77 or left ≥1.65) were categorized as having high carotid FDG uptake. Those with CIMT over the 75th percentile (right or left ≥0.75 mm) were categorized as having high CIMT.

Based on M-TBR, 363 subjects had high carotid FDG uptake, whereas 726 had low FDG uptake. The clinical characteristics of high and low carotid FDG uptake groups are summarized in Table 1. The high FDG group had significantly older age, body mass index, waist circumference, low-density lipoprotein cholesterol, hypertension prevalence, number of atherosclerotic plaques, and CIMT than the low FDG uptake group. Importantly, the high FDG uptake group had a

**TABLE 1 Characteristics of Study Subjects Stratified by Magnitude of Carotid FDG Uptake**

| | High Carotid FDG (n = 363) | Low Carotid FDG (n = 726) | p Value |
|---|---|---|---|
| Age, yrs | 53.2 ± 7.6 | 51.1 ± 5.5 | <0.000 |
| Male | 343 (94.5) | 693 (95.5) | 0.550 |
| Hypertension | 94 (26.0) | 148 (20.4) | 0.044 |
| Diabetes mellitus | 34 (9.4) | 71 (9.8) | 0.913 |
| Current smoking | 133 (36.7) | 238 (33.1) | 0.249 |
| Obesity | 168 (46.3) | 282 (38.8) | 0.022 |
| Metabolic syndrome | 64 (17.6) | 104 (14.3) | 0.156 |
| Carotid plaque | 174 (47.9) | 289 (39.8) | 0.011 |
| Systolic BP, mm Hg | 119.9 ± 16.2 | 118.4 ± 15.4 | 0.152 |
| Hemoglobin $A_{1c}$, % | 5.7 ± 0.5 | 5.7 ± 0.6 | 0.813 |
| FPG, mg/dl | 96.9 ± 15.1 | 97.7 ± 19.5 | 0.498 |
| LDL-C, mg/dl | 125.7 ± 28.5 | 120.0 ± 28.0 | 0.002 |
| HDL-C, mg/dl | 49.2 ± 11.8 | 51.0 ± 12.6 | 0.022 |
| Triglyceride, mg/dl | 145.1± 66.3 | 139.6 ± 77.4 | 0.253 |
| Body mass index, kg/$m^2$ | 24.8 ± 2.2 | 24.3 ± 2.5 | 0.004 |
| Waist circumference, cm | 87.0 ± 6.3 | 85.2 ± 7.0 | <0.000 |
| hsCRP, mg/l | 1.1 ± 2.0 (0.6, 0.3-1.1) | 1.2 ± 2.5 (0.5, 0.3-1.0) | |
| Estimated GFR, ml/min | 82.2 ± 12.7 | 84.4 ± 13.1 | 0.009 |
| Framingham Risk Score, % | 13.9 ± 9.9 | 11.4 ± 7.7 | <0.000 |
| CIMT, mm | 6.8 ± 1.8 | 6.4 ± 1.2 | <0.000 |
| Duration of follow-up, yrs | 4.3 ± 0.9 | 4.2 ± 1.0 | 0.456 |
| M-TBR | 1.76 ± 0.1 | 1.51 ± 0.1 | <0.000 |
| $SUV_{max}$ | 1.73 ± 0.1 | 1.55 ± 0.1 | <0.000 |
| Events | 12 (3.3) | 7 (1.0) | 0.011 |

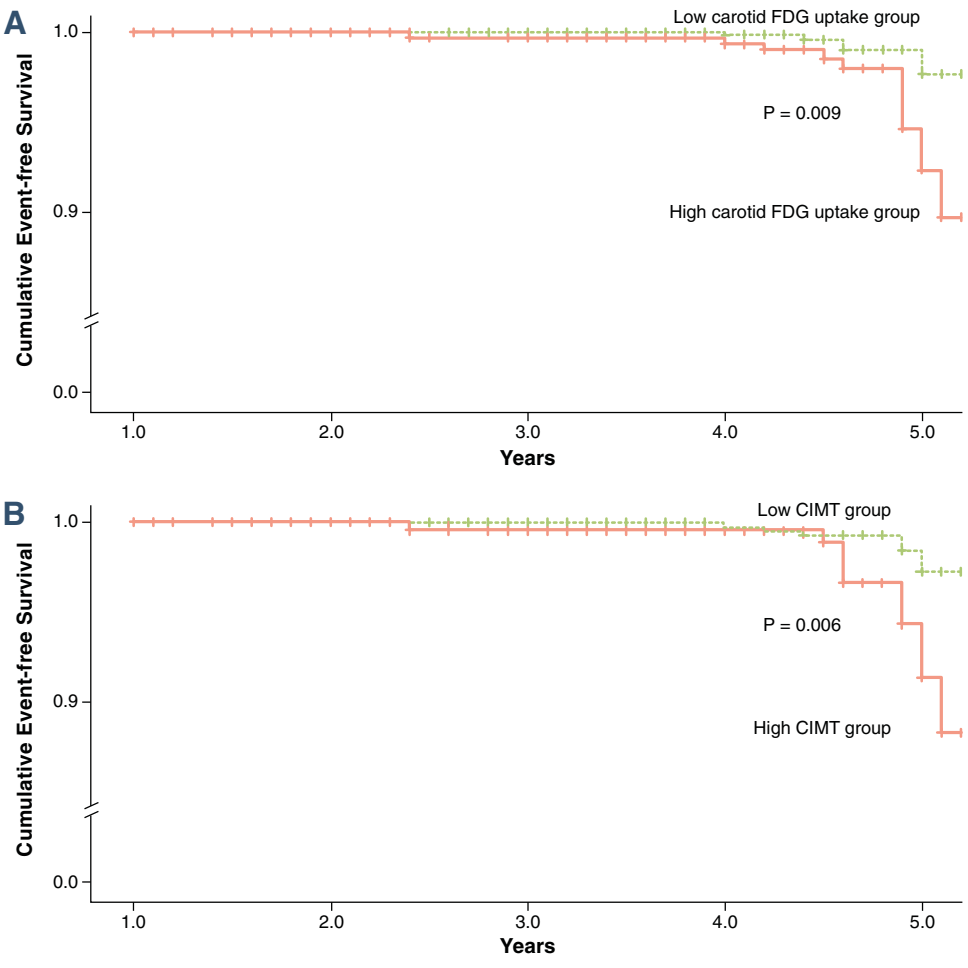
Values are mean ± SD, n (%), or mean ± SD (median, interquartile range).

BP = blood pressure; CIMT = carotid intima-media thickness; FDG = fluoro-2-deoxyglucose; FPG = fasting plasma glucose; GFR = glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; hsCRP = high sensitive C-reactive protein; LDL-C = low-density lipoprotein cholesterol; M-TBR = maximal target-to-blood pool ratio; $SUV_{max}$ = maximal standard uptake value.

significantly higher FRS (13.9 ± 9.9% vs. 11.4 ± 7%; p < 0.000) and higher incidence of cardiocerebrovascular events (3.3% vs. 1.0%; p = 0.011) compared with the low FDG uptake group (**Figure 1**). The difference in cardiocerebrovascular event rate between the 2 groups was significant in the high CIMT category, whereas it did not reach statistical significance in the low CIMT category (**Figure 2**).

**CARDIOCEREBROVASCULAR EVENTS AND COX REGRESSION.** Over a mean follow-up period of 4.2 ± 1.0 years (range 1 to 5.5 years), 19 of 1,089 subjects (1.74%) experienced cardiocerebrovascular events (Online Table 1); there were 3 myocardial infarctions (0.27%), 8 cases of angina pectoris (0.73%), 3 cases of silent myocardial ischemia (0.27%), 3 ischemic strokes (0.27%), and 2 transient cerebral ischemic attacks (0.18%). All 3 subjects in whom silent ischemia developed were confirmed to have coronary artery stenosis by coronary angiography (Online Table 1). All 8 patients in whom angina developed also underwent coronary angiography (Online Table 1). Of these, coronary artery stenosis was confirmed in 6 subjects. Another subject had a positive exercise test and underwent a percutaneous coronary intervention in another hospital. The remaining patient had exercise-induced chest pain and a positive treadmill test. Although coronary angiography did not show significant stenosis, microvascular dysfunction was suspected. However, this patient actually belonged to the low FDG uptake group. One 49-year-old subject with focal carotid FDG

**FIGURE 1 Kaplan-Meier Curves for Cardiocerebrovascular Events**




Comparison of cumulative event-free survival rates between groups stratified by carotid FDG uptake **(A)** and carotid intima-media thickness **(B)**. Differences between groups were analyzed by log-rank tests. CIMT = carotid intima-media thickness; FDG = fluoro-2-deoxyglucose.

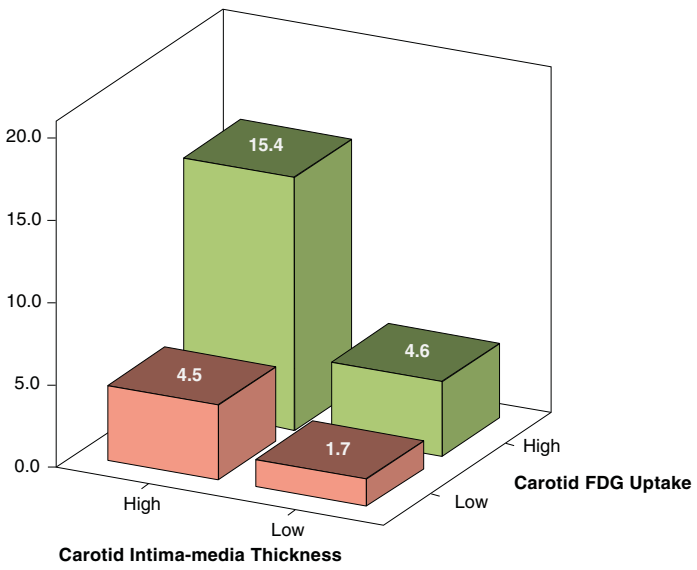
uptake died during follow-up. However, this was not included as a vascular event because the cause of death was unknown. When subjects with events were divided according to FDG uptake, there was no difference in demographic and clinical characteristics (Online Table 2).

On univariate analysis, Cox regression demonstrated a significant association of high CIMT, high hsCRP, and high FDG uptake with increased cardiocerebrovascular events (**Table 2**). The association of carotid plaques with events approached significance. The FRS and other traditional risk factors used as categorical variables failed to show a statistically significant association with events. Multivariate analysis that included significant univariate factors revealed that high CIMT (hazard ratio: 2.82, 95% confidence interval: 1.13 to 7.03; p = 0.026) and high FDG uptake (hazard ratio: 2.98, 95% confidence interval: 1.17 to 7.62; p = 0.022) were significant independent predictors of cardiocerebrovascular events (**Table 2**).

**PREDICTIVE VALUE AND NET RECLASSIFICATION.** We next performed a time-dependent AUC analysis to compare the discrimination capacities of cardiocerebrovascular event prediction models that included the FRS at baseline with or without the addition of carotid FDG, CIMT, and hsCRP information. The addition of carotid FDG uptake to the FRS significantly improved predictive performance, as measured by the AUC that increased from 0.60 to 0.73 (p = 0.04), whereas the addition of CIMT or hsCRP did not (**Table 3**). Furthermore, improvements of AUC by the addition of carotid FDG uptake to the FRS plus CIMT model (from 0.65 to 0.75, p = 0.07), the FRS plus hsCRP model (from 0.62 to 0.74, p = 0.061), and the FRS plus CIMT plus hsCRP model (from 0.65 to 0.74, p = 0.07) (**Table 3**) approached statistical significance.

Net reclassification for event prediction was also improved by the addition of carotid FDG uptake to the FRS plus hsCRP (NRI, 40.1%; p = 0.04), and improvement approaching significance was achieved by the addition of carotid FDG uptake to the FRS (NRI, 40.1%; p = 0.06), as well as the FRS plus CIMT (NRI, 32.9%; p = 0.07) (**Table 3**). IDI results for adding carotid FDG uptake to models including the FRS, CIMT, and hsCRP are also shown in **Table 3**.

**FIGURE 2** **Cardiocerebrovascular Event Rate per 1,000 Person-Years Adjusted by FDG Uptake Level and CIMT Measurement**




Event rates between high and low FDG uptake groups were significantly different in the high CIMT category (p = 0.047), whereas it did not reach statistical significance in the low CIMT category (p = 0.116). Abbreviations as in **Figure 1**.

## DISCUSSION

In this cohort of asymptomatic adults, high carotid FDG uptake was a significant and independent predictor of cardiocerebrovascular events and improved discrimination of risk prediction when added to the FRS with or without CIMT information.

Inflammation contributes to the progression of vulnerable plaques and causes their instability (1). As such, arterial inflammation is closely associated with cardiocerebrovascular events (1–3), and several reports demonstrate inflammatory cell infiltration in coronary and carotid plaques of patients with acute coronary syndrome or stroke (27–29). Accordingly, biomarkers of inflammation are emerging as promising indicators of cardiovascular prognosis. However, there is also a growing need to validate the precise clinical values of these indicators. Increased FDG uptake in atherosclerotic vessels has been shown to represent unstable inflammatory plaques (12,13), and carotid endarterectomy tissues demonstrate that these areas correlate with infiltrating macrophages (12). These findings indicate that FDG PET has the ability to monitor the inflammatory component of atherosclerotic plaques and suggest a role for predicting cardiovascular risk. Serum hsCRP is another useful biomarker of inflammatory response that can help to assess progression of atherosclerosis toward myocardial infarction and stroke (30–33). However, hsCRP can be increased by a myriad of causes other than arterial inflammation and is unable to discriminate the inflammation site as is possible with

**TABLE 2 Cox Regression Analysis for Risk Factors Associated With Cardiocerebrovascular Events**

| | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | p Value | HR | 95% CI | p Value |
| High CIMT | 3.28 | 1.33–8.08 | 0.010 | 2.82 | 1.13–7.03 | 0.026 |
| High FDG uptake | 3.25 | 1.22–08.25 | 0.013 | 2.98 | 1.17–07.62 | 0.022 |
| High hsCRP (>3.0 mg/l) | 3.16 | 1.04–09.58 | 0.042 | 2.71 | 0.88–8.36 | 0.081 |
| Carotid plaques | 2.44 | 0.92–06.44 | 0.071 | | | |
| High FRS (>20%) | 2.00 | 0.72–05.57 | 0.183 | | | |
| Low HDL-C (<40 mg/dl) | 1.83 | 0.69–04.83 | 0.221 | | | |
| Hypertension | 1.77 | 0.69–04.52 | 0.229 | | | |
| Age (>50 yrs) | 1.55 | 0.59–04.09 | 0.370 | | | |
| Central obesity (WC ≥90 cm) | 1.55 | 0.51–04.68 | 0.436 | | | |
| Obesity (BMI ≥25 kg/m$^2$) | 1.42 | 0.57–03.49 | 0.446 | | | |
| Diabetes mellitus | 0.65 | 0.19–02.24 | 0.495 | | | |
| High LDL-C (>130 mg/dl) | 1.29 | 0.52–03.22 | 0.581 | | | |
| Metabolic syndrome | 0.77 | 0.26–02.34 | 0.652 | | | |
| Male | 0.77 | 0.10–05.86 | 0.804 | | | |
| Current smoking | 0.97 | 0.37–02.57 | 0.960 | | | |

BMI = body mass index; CI = confidence interval; FRS = Framingham risk score; HR = hazard ratio; WC = waist circumference.

FDG PET. Furthermore, it was previously shown that hsCRP and carotid FDG uptake provide distinct prognostic information (19).

There have been a limited number of studies that evaluated the relationship of arterial FDG uptake with vascular events (16–18). The study by Paulmier et al. (16) compared 45 cancer patients with increased arterial FDG uptake with 56 without increased uptake and observed more cardiovascular events in the former group. In another study by Rominger et al. (17) retrospectively evaluated FDG PET/CT findings in 932 cancer patients and observed a significant association between arterial FDG uptake and subsequent vascular events. However, these studies were performed on cancer patients whose vascular pathology could be influenced by systemic anticancer therapies. In addition, follow-up was limited to short durations. Most importantly, these studies were unable to compare the prognostic value of carotid FDG uptake with that of traditional risk factors. Recently, Figueroa et al. (18) evaluated 513 cancer-free individuals and demonstrated that FDG uptake in large vessels such as the ascending aorta and superior vena cava improves prediction of cardiovascular events beyond the FRS (18). However, the clinical significance of FDG uptake in the carotid artery is likely to be considerably different from that of large vessels. Our study was performed on a large cohort of asymptomatic adults and demonstrates that increased carotid FDG uptake is an independent predictor of vascular events that outperforms traditional cardiovascular risk factors.

In our results, the addition of carotid FDG information to the FRS significantly increased the time-dependent AUC, indicating improved predictive power. In contrast, addition of CIMT, which has been advocated to improve prediction of individual cardiovascular risk (34), did not significantly increase the time-dependent AUC. This finding is in agreement with a recent large-scale meta-analysis in which addition of CIMT to the FRS only showed a trend for improving risk prediction that was not considered to be of clinical importance (35). In our study, the addition of carotid FDG uptake to the FRS plus CIMT tended to improve the time-dependent AUC in a manner that approached significance. Inclusion of carotid FDG uptake information with the FRS may thus have the potential to improve prediction of future vascular events from poor (AUC <0.70) to acceptable (or good) (AUC ≥0.70).

Our NRI results showed that 40.1% and 32.9% more subjects were appropriately reclassified than

**TABLE 3 Comparison of Various Models Using AUC, NRI, and IDI**

| Model | Time-Dependent AUC* | NRI† | IDI† |
|---|---|---|---|
| FRS vs. FRS+CIMT | 59.9 (45.0 to 74.9) vs. 65.1 (48.5 to 81.8), 0.333 | 28.9 (−4.9 to 50.0), 0.080 | 3.3 (0.2 to 14.7), 0.007 |
| FRS vs. FRS+FDG | 59.9 (45.0 to 74.9) vs. 73.2 (60.3 to 86.2), 0.039 | 40.1 (−1.3 to 58.4), 0.060 | 0.6 (−0.1 to 2.4), 0.110 |
| FRS vs. FRS+hsCRP | 59.9 (45.0 to 74.9) vs. 62.1 (46.9 to 77.3), 0.438 | 17.8 (−9.7 to 45.6), 0.179 | 0.1 (0.0 to 0.6), 0.219 |
| FRS vs. FRS+CIMT+FDG | 59.9 (45.0 to 74.9) vs. 74.6, (59.7 to 89.5), 0.046 | 40.4 (−1.2 to 59.8), 0.053 | 3.6 (0.5 to 18.5), <0.001 |
| FRS vs. FRS+hsCRP+FDG | 59.9 (45.0 to 74.9) vs. 73.7 (60.5 to 87.0), 0.044 | 38.8 (0.0 to 57.7), 0.020 | 0.8 (0.0 to 3.6), 0.033 |
| FRS+CIMT vs. FRS+FDG | 65.1 (48.5 to 81.8) vs. 73.2 (60.3 to 86.2), 0.188 | 28.0 (−20.7 to 49.5), 0.246 | 0.8 (−0.3 to 3.7), 0.219 |
| FRS+hsCRP vs. FRS+FDG | 62.1 (46.9 to 77.3) vs. 73.2 (60.3 to 86.2), 0.080 | 40.4 (−14.4 to 58.9), 0.106 | 0.5 (−0.1 to 2.4), 0.146 |
| FRS+CIMT vs. FRS+CIMT+FDG | 65.1 (48.5 to 81.8) vs. 74.6 (59.7 to 89.5), 0.066 | 32.9 (−1.8 to 54.8), 0.073 | 0.3 (−0.2 to 2.4), 0.219 |
| FRS+hsCRP vs. FRS+hsCRP+FDG | 62.1 (46.9 to 77.3) vs. 73.7 (60.5 to 87.0), 0.061 | 40.1 (0.0 to 58.0), 0.040 | 0.7 (0.0 to 2.9), 0.033 |
| FRS+CIMT+hsCRP vs. FRS+CIMT+hsCRP+FDG | 64.8 (47.9 to 81.7) vs. 74.2 (59.3 to 89.1), 0.070 | 32.9 (−2.8 to 53.9), 0.073 | 0.4 (−0.2 to 2.9), 0.166 |

*Values are % (95% confidence interval) vs. % (95% confidence interval), p value. †Values are % (95% confidence interval), p value.
AUC = area under the receiver-operating characteristic curve; IDI = integrated discrimination improvement (at 4 years); NRI = (continuous) net reclassification index; other abbreviations as in Tables 1 and 2.

inappropriately reclassified when carotid FDG uptake was added to the FRS and the FRS plus CIMT, respectively. These results indicate that carotid inflammation as demonstrated by FDG PET/CT improves prediction of cardiovascular risk beyond that provided by the FRS and CIMT. Changes in IDI by the addition of carotid FDG to the FRS or the FRS plus CIMT were relatively small (<1%). As this index indicates how far individuals are moved along the range of predicted risk, this implies that even though there were significant improvements in net reclassification by the addition of carotid FDG uptake, the magnitude of change in predicted risk was small. However, this is to be expected when the population has low baseline risk as in our study subjects.

On average, our study cohort had an FRS of 12.2 ± 8.6%, which is categorized as intermediate cardiovascular risk. However, the overall cardiocerebrovascular event rate was 1.7% over a period of 4.2 years, which translates into an estimated 10-year risk of 4.0%. The relatively low rate of events in our study is likely contributed to by the characteristics of the participants in our health screening program, who were health-conscious and motivated individuals of high socioeconomic status. When this population was categorized according to PET results, the estimated 10-year event rate was 7.7% for subjects with high carotid FDG uptake and 2.4% for those with low FDG uptake. A recent guideline reported that the estimated 10-year risk of a first cardiovascular event is <5% in approximately one-half of asymptomatic individuals (36). Therefore, FDG PET/CT may be able to substratify the likelihood of cardiovascular events in asymptomatic individuals into groups with 10-year risks greater or lower than 5%.

Notwithstanding the value of carotid FDG uptake for predicting subsequent vascular events shown in this study, there are obvious difficulties in applying this finding to clinics. This includes the limited accessibility and cost of PET/CT studies and potential radiation burdens. PET screenings in this study were part of a health checkup program to screen the whole body for possible hidden malignancy. FDG PET/CT is performed in some countries or institutions for individuals who have reason to be anxious about the possibility of hidden tumors, even though it is not generally recommended for cancer screening. Therefore, it should be mentioned that generation of our study population is from a limited and specific setting. However, there are several practical occasions when an individual's carotid FDG uptake can be assessed. The most common situation is when subjects undergo FDG PET/CT for a suspected tumor or surveillance for a possible disease recurrence.

**STUDY LIMITATIONS.** First, the relatively small number of vascular events provides suboptimal statistical power for robust analysis. Some prognostic parameters showed a trend for improvement by the addition of carotid FDG uptake but did not reach statistical significance, likely due to an insufficient number of events. Also, the method of follow-up for events was limited to review of medical records. In addition, the study population was predominantly health-conscious Korean adult males, allowing the potential for selection-related bias that may restrict generalization of the study results. Therefore, larger prospective studies in various populations with long-term follow-up and a greater number of events are warranted to confirm the findings of this study.

## CONCLUSIONS

High carotid FDG uptake in asymptomatic adults is associated with a significantly increased risk for cardiocerebrovascular events independent of traditional risk factors. Further studies are thus warranted to confirm the additional value of this indicator to improve risk prediction.

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## PERSPECTIVES

**COMPETENCY IN MEDICAL KNOWLEDGE:** In asymptomatic individuals, increased carotid FDG uptake is an independent predictor of future cardiocerebrovascular events. Furthermore, this indicator improves discrimination of risk prediction when added to the FRS with or without CIMT information.

**TRANSLATIONAL OUTLOOK:** Additional studies are needed to validate whether such imaged-guided carotid FDG uptake approach can be used to help modify risk and future cardiovascular events in asymptomatic individuals.

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**KEY WORDS** cardiovascular events, carotid artery, $^{18}$F-FDG, prognosis, risk prediction

**APPENDIX** For supplemental tables, please see the online version of this article.