

# Metabolic imaging: imaging plaques

Francis R. Joshi, Mohammed Chowdhury, James H. F. Rudd

Division of Cardiovascular Medicine, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK

Correspondence: Dr. James H. F. Rudd, Box 110, Level 6, ACCI,  
Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ, UK  
Tel: +44 (0)1223 331504, fax: +44 (0)1223 331505, e-mail: jhfr2@cam.ac.uk

## Abstract

Atherosclerosis is an inflammatory disease that causes most myocardial infarctions. Able to highlight areas of high glucose metabolism, PET imaging using FDG has been advocated as a means of measuring inflammation in the arterial wall. FDG uptake is correlated with the number of cardiovascular risk factors, and emerging evidence suggests that it may play a role in the prediction of risk for future cardiovascular events. While the determinants of vascular FDG uptake are still the focus of study, this imaging technique is reproducible and is increasingly being used to test novel anti-atherosclerotic drugs in phase II clinical trials. This review will outline the evidence base, shortcomings and emerging applications for FDG-PET in vascular imaging. Alternative, potentially more specific, PET tracers for measuring vascular inflammation will also be discussed. ■ Heart Metab; 2013;60:15–21

**Keywords:** Atherosclerosis; fluorodeoxyglucose; inflammation, non invasive imaging.

## Introduction

Non invasive imaging of atherosclerosis ideally aims to provide novel insight into the underlying biology of the disease, a means to track the effects of drug therapies and value in the assessment of at-risk individuals.

PET is attractive because of its molecular sensitivity; picomolar levels of tracer can be detected at a target site, though spatial resolution is limited (3–5 mm). Co-registration with CT or MRI is needed to localize PET tracer uptake to underlying anatomy. PET imaging involves ionizing radiation, precluding its use for population screening. Nevertheless, imaging with FDG-PET has made considerable progress towards the above goals. This review will outline the evidence for its use in clinical imaging.

## Imaging inflammation with FDG

FDG, a glucose analogue, competes with endogenous glucose for facilitated transport sites and after phosphorylation becomes trapped within cells. This accumulation can then be imaged and quantified in the PET scanner. FDG-PET is the gold standard im-

aging modality for the detection of tumor metastases in oncology, wherein it exploits the higher metabolic demands of cancer cells. Vascular FDG uptake was thus first noted in patients undergoing PET for cancer staging [1]. FDG is the most commonly used tracer in PET imaging of atherosclerosis. Although uptake is not specific for inflammatory cells, it exploits the fact that macrophages have higher glucose metabolism than both surrounding cells and healthy artery wall [2].

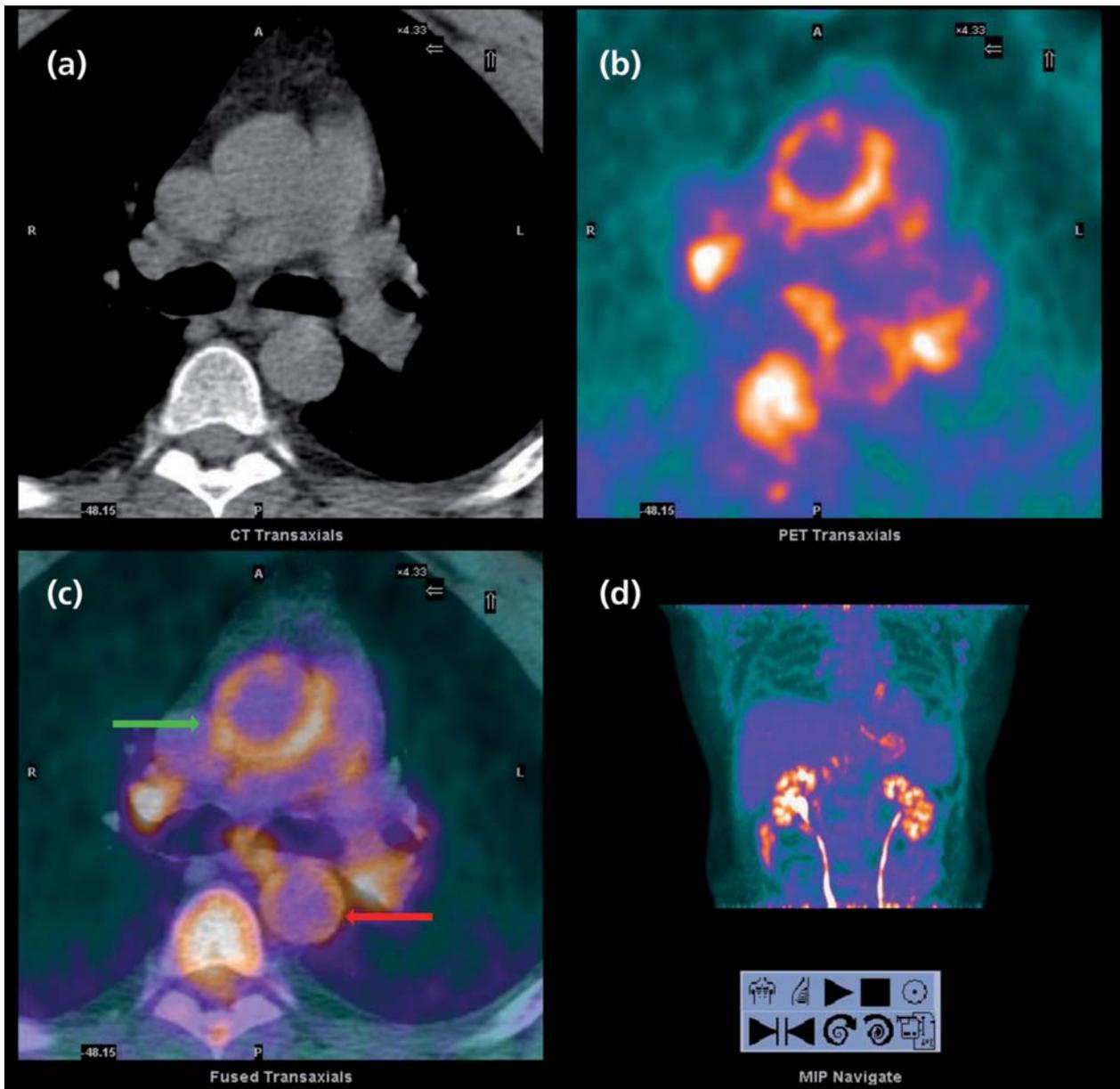
## Imaging protocols and analysis

Techniques and methods of image analysis of FDG-PET for atherosclerosis have not yet been standardized [3]. Patients are required to fast before imaging. [<sup>18</sup>F] has a half-life of 110 minutes, and a typical dose of approximately 250 MBq is injected intravenously and allowed to circulate. The circulation time (90–180 minutes) is generally longer than for oncological examinations to allow for accumulation into the diseased vascular wall and adequate clearance of blood pool activity, creating favourable TBR [4] (*Figure 1*).

**ABBREVIATIONS**

**BMI:** Body Mass Index; **Bq:** Becquerel; **CT:** Computed Tomography; **DOTATATE:** [1,4,7,10-tetraazacyclododecane-N, N', N'', N'''-tetraacetic acid]-D-Phe1,Tyr3-octreotate; **FDG:** [18F]-2-fluoro-2-deoxyglucose; **MI:** Myocardial Infarction; **MRI:** Magnetic Resonance Imaging; **PET:** Positron Emission Tomography; **SUV:** Standardized Uptake Value; **TBR:** Target-to-Background Ratio; **TIA:** Transient Ischaemic Attack

Different methods have been proposed to quantify FDG uptake in atherosclerosis. The SUV, which is the decay-corrected tissue concentration of FDG (in kBq/g), corrected for injected FDG dose and lean body mass, is a widely accepted method that does not require plasma sampling. Correction (by division) for blood pool (venous) activity produces a TBR. TBR has been shown to correlate better with underlying macrophages than maximum SUV [5].



**Fig. 1** Imaging vascular inflammation with FDG-PET/CT. (a) Transaxial CT image of the ascending aorta at the level of the main pulmonary artery. (b) Corresponding transaxial FDG-PET image at the same location. (c) Fused PET/CT image allowing for anatomical co-localization of FDG uptake. Circumferential uptake is noted in both the ascending aorta (green arrow) and the descending aorta (red arrow). (d) Coronal FDG-PET image in the same patient. There is relatively little myocardial uptake in this case, while renal excretion of the tracer is noted. CT, computed tomography; FDG, [18F]-2-fluoro-2-deoxyglucose; PET, positron emission tomography.

**Imaging human atherosclerosis with FDG**

In the first prospective study in humans, levels of inflammation measured as accumulation rate of FDG were 27% greater in the culprit carotid after recent stroke or transient ischemic attack (TIA) than in the contralateral vessel [6] (*Figure 2*). Ex-vivo imaging by micro-PET (resolution 1 mm) has confirmed heterogeneous uptake within carotid plaques, with “hot spots” of uptake co-localizing with regions of intense macrophage infiltration [7]. FDG uptake is independent of plaque thickness, area or luminal stenosis [5] and is linked to male sex, age, smoking, the metabolic syndrome [8] and type 2 diabetes [9] (*Figure 3*). FDG-PET is a reproducible measure, valid across several vascular beds with excellent short-term and interobserver reproducibility [10].

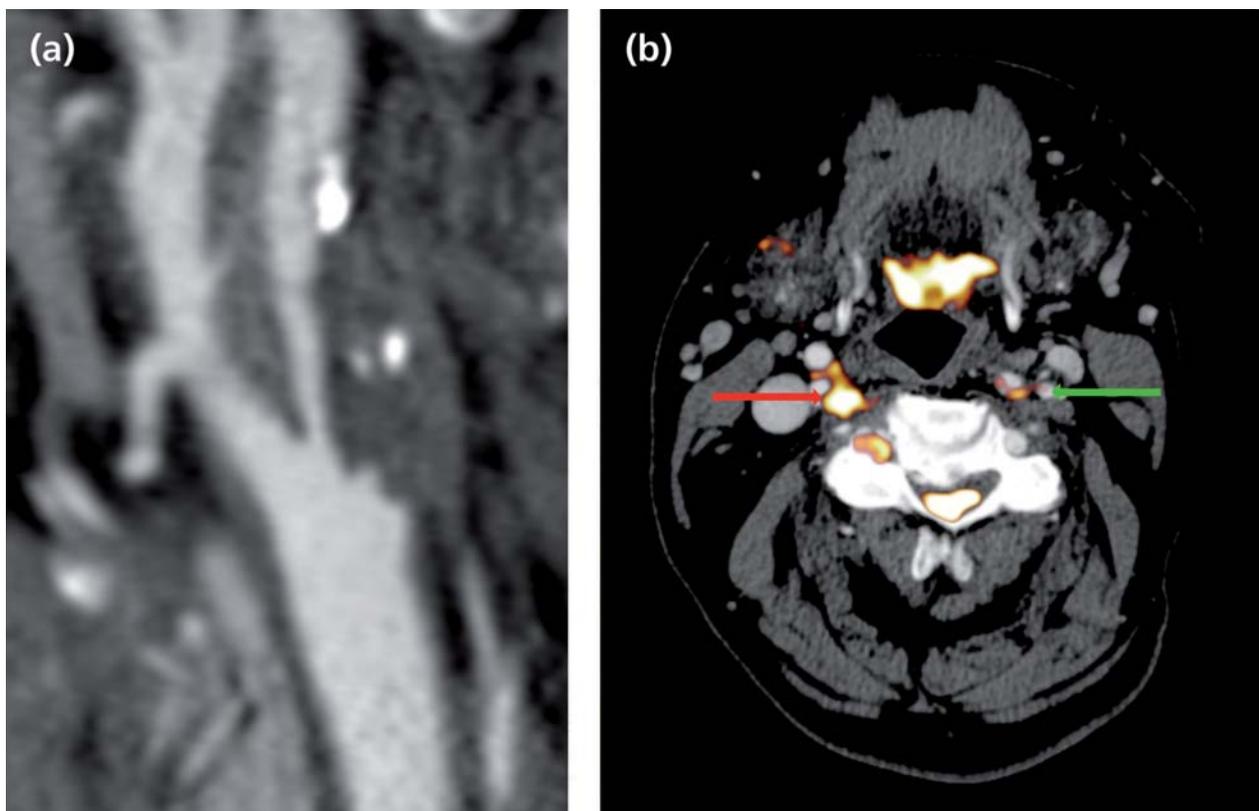
There is evidence that plaque metabolic activity correlates with high-risk anatomical features within atherosclerotic plaques. Large lipid cores on carotid MRI and increasing numbers of high-risk markers (low attenuation plaque, surface irregularity and positive remodeling) on carotid CT angiography have higher FDG uptake

than more stable phenotypes [11, 12]. FDG uptake can distinguish between culprit carotid and vertebral lesions in posterior circulation stroke [13], and in the carotid artery uptake correlates with microembolic signals on transcranial Doppler ultrasound after TIA [14].

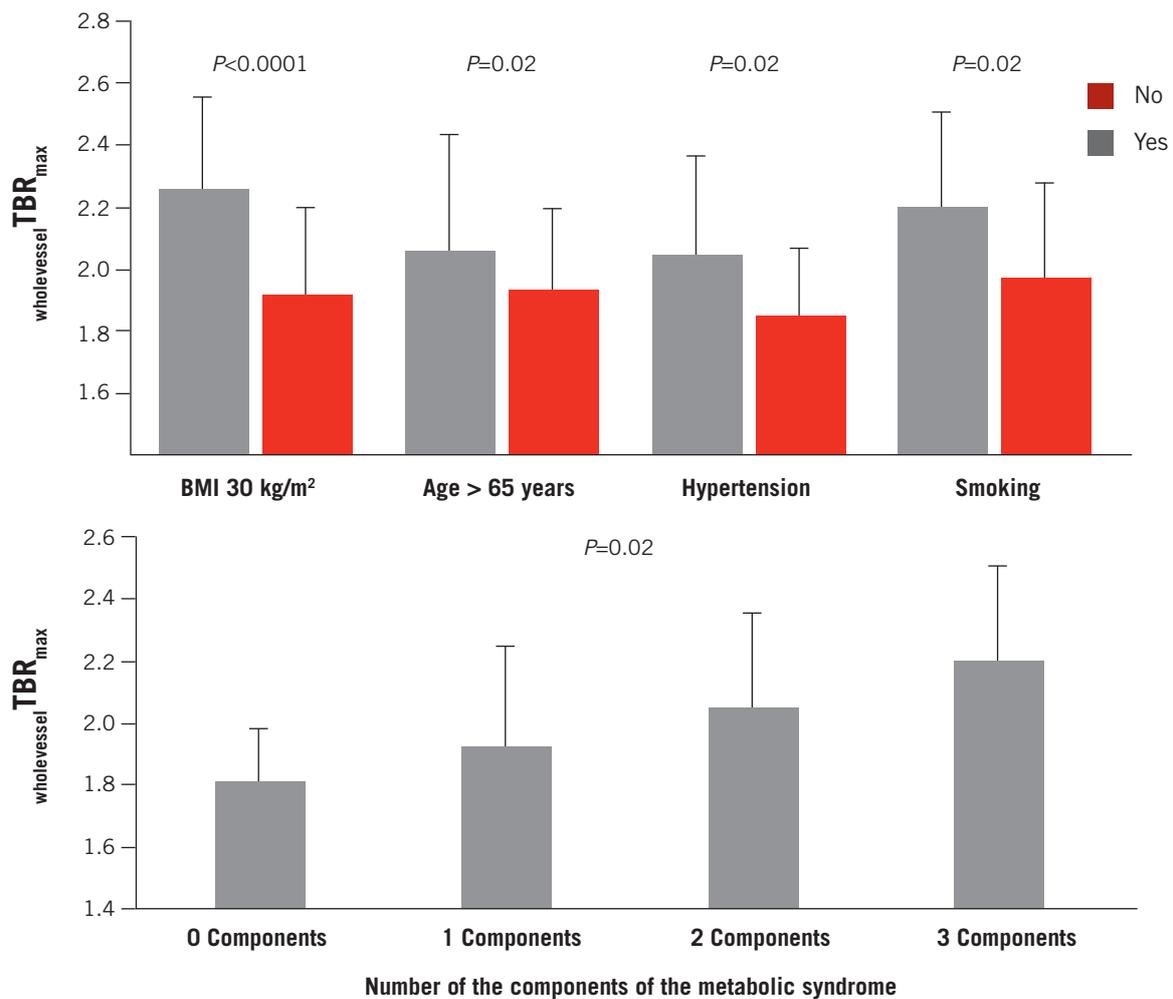
**Determinants of vascular FDG uptake**

Autoradiography with tritiated deoxyglucose was shown to co-localize with macrophages in explanted carotid plaque [6]. Tawakol et al [5] demonstrated a very strong correlation of in-vivo imaging with macrophage staining, and suggested that uptake was independent of smooth muscle cell content. FDG uptake is thought to reflect activation status of macrophages; recent in-vitro data suggest that increased uptake may reflect early foam cell development [15].

However, both the cellular microenvironment and delivery of tracer via intraplaque neovessels [16] are also likely to be important contributors to the observed signal. Hypoxia is known to exist within atherosclerotic plaques [17]. Hypoxia leads to increased glycolysis, up-



**Fig. 2** FDG-PET/CT imaging in symptomatic carotid atherosclerosis. (a) CT angiography: three-dimensional multiplanar reformatted image of a severely stenosed right internal carotid artery 1 week after an acute cerebrovascular event in a 69-year-old man. (b) FDG-PET: transaxial image of PET co-registered to CT angiography in the same patient. Intense tracer uptake is noted in the culprit right internal carotid artery (red arrow). Lesser uptake is noted in the left internal carotid artery (green arrow). CT, computed tomography; FDG, [<sup>18</sup>F]-2-fluoro-2-deoxyglucose; PET, positron emission tomography.



**Fig. 3** Vascular risk factors and carotid arterial FDG uptake. (a) Clinical risk factors and carotid vessel wall inflammation in patients with coronary artery disease. The presence of a body mass index of 30 kg/m<sup>2</sup> or greater, age greater than 65 years, hypertension and smoking are independent predictors for the maximum whole-vessel TBR (wholevesselTBR<sub>max</sub>). (b) Relationship between the components of the metabolic syndrome and the same measure of carotid arterial FDG uptake. BMI, body mass index; FDG, [<sup>18</sup>F]-2-fluoro-2-deoxyglucose; TBR, target-to-background ratio. (From Bucerius et al [8] with permission).

regulation of glucose transporters, promotes the development of foam cells [18], adversely affects macrophage lipid metabolism [19], and drives neoangiogenesis and further inflammatory responses, all of which may influence in-vivo FDG imaging [20]. Further studies are required for clarification of how important these effects are in clinical imaging.

#### Intervention studies with vascular FDG imaging

Because of the central role of inflammation in atherosclerosis, and the number of therapies that aim to reduce it, increasingly, arterial FDG-PET/CT imaging is being applied for the early assessment of anti-atherosclerosis therapy. Treatment with statins demonstrated signal reduction after only 3 months' therapy [21]. The recent dal-PLAQUE trial with dalcetrapib has further

demonstrated the value of FDG-PET for this purpose, providing evidence of vascular safety (ie, no increase in inflammation) versus placebo at 6 months with this novel agent [22].

#### Coronary artery imaging

Imaging coronary artery atherosclerosis presents special challenges. These arteries are smaller than the resolution of PET. Imaging is hindered by respiratory and cardiac motion during the time taken to acquire a PET dataset, typically around 20 minutes. Finally, FDG is taken up avidly by myocardium, which preferentially metabolizes glucose over free fatty acids.

Attempts to switch myocardial metabolism to free fatty acids by dietary manipulation before imaging have had varying success. In a study of [<sup>18</sup>F]-sodium fluoride

and FDG uptake in the coronary arteries of patients with aortic stenosis, and using overnight fasting to suppress myocardial uptake, only 50% of coronary segments were analyzable [23]. By gating for cardiac motion, in addition to dietary manipulation, fasting and intravenous heparin, Cheng et al [24] were able to demonstrate increased culprit site FDG uptake more commonly in patients with acute MI than in patients with stable angina. However, even this approach failed to suppress myocardial FDG uptake adequately in 11 of 27 patients and failed to detect increased signal at the culprit site in nearly half of patients after MI [24]. It seems likely that imaging inflammation in coronary plaques will require more macrophage-specific tracers than FDG.

### Molecular imaging of vascular inflammation: alternatives to FDG

Many promising tracers already have applications in oncology. These include radiolabeled choline, taken up and integrated into cell membranes in tumor cells and macrophages. [11C]-choline was not taken up into normal vascular wall, or purely calcified lesions, in a retrospective analysis of 93 male patients undergoing cancer imaging [25].

Coronary artery uptake has been described for the somatostatin receptor analogue [68Ga]-DOTATATE in the left anterior descending coronary artery, correlating with previous cardiovascular events [26]. More recently, a retrospective study of cancer imaging has demonstrated [68Ga]-DOTATATE uptake in large arteries, including the carotids, correlating with the presence of calcified plaques, age, hypertension and vas-

cular FDG uptake [27]. Concordant vascular uptake of both tracers was only seen in a minority of the cases reviewed, and it has been suggested that this may reflect greater specificity of [68Ga]-DOTATATE for proinflammatory macrophages (*Figure 3*). Further studies are awaited.

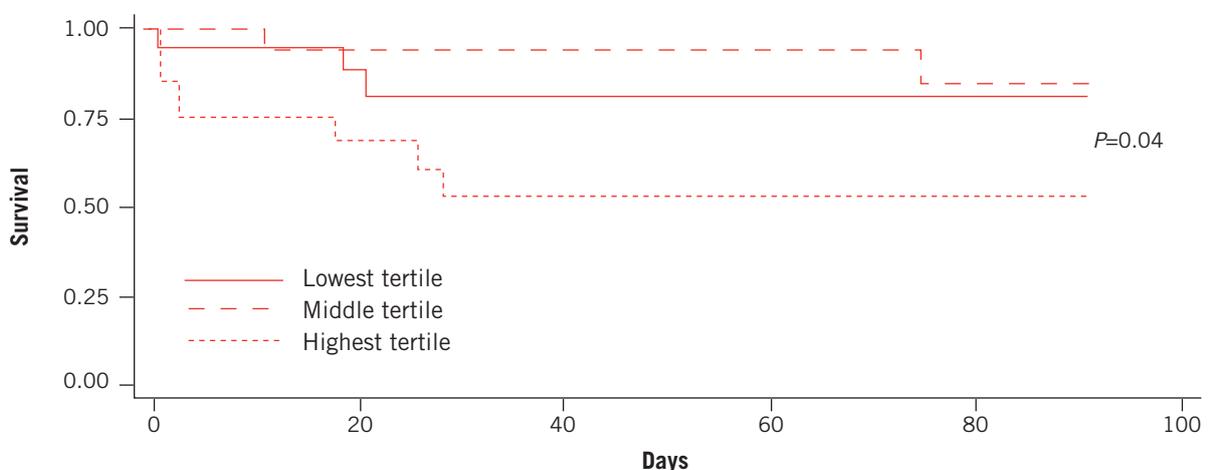
### Prognostic implications of vascular FDG uptake

In retrospective analyses of patients undergoing PET for oncology staging, high levels of baseline vascular FDG uptake were associated with subsequent cardiovascular events [28]. In a prospective series of 60 patients after TIA and stroke, Marnane et al [29] have shown that uptake of FDG into carotid plaque predicts recurrent stroke independently of the degree of stenosis (*Figure 4*). The authors were able to define thresholds of FDG uptake to identify accurately the risk of recurrent stroke: maximum SUV values greater than 3.33 conferred a 14-fold increase in the accuracy of the clinical estimate of this outcome. In addition, because some of these patients will have undergone endarterectomy, it is likely that this figure represents an underestimate of the predictive power of FDG-PET. These data need further validation but suggest FDG may play a role in the selection of candidates for endarterectomy.

The results of prospective event-driven studies are awaited, including the BiImage Study that aims to identify imaging markers (CT, MRI and FDG-PET/CT) of future cardiovascular risk in asymptomatic patients [30].

### Conclusions

Non invasive imaging of atherosclerosis is needed to investigate the underlying biology, identify at-risk individ-



**Fig. 4** FDG imaging of culprit carotid arteries predicts recurrent stroke. Kaplan-Meier survival estimate (freedom from recurrent stroke) by tertiles of maximum standardized uptake. FDG, [18F]-2-fluoro-2-deoxyglucose. (From Marnane et al. [29] with permission).

uials and test novel anti-atherosclerotic therapies. Vascular imaging with FDG in both preclinical models and human subjects has provided considerable insight into pathophysiology. The technique is reproducible enough to test new treatments in phase II clinical trials. Nevertheless, its main limitation, namely a lack of specificity, is acknowledged. Ongoing work will define the extent to which hypoxia is a determinant of the observed uptake into atherosclerotic plaque. More specific tracers will probably be needed to image inflammation in the coronary circulation.

Finally, although prospective data regarding its value for risk prediction are awaited, the ionizing radiation associated with vascular PET imaging will probably limit its application for widespread screening of asymptomatic individuals. ■

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