

EDITORIAL COMMENT

## In Vivo Evaluation of Atherosclerotic Plaque Inflammation and of Anti-Inflammatory Effects of Statins by $^{18}\text{F}$ -Fluorodeoxyglucose Positron Emission Tomography\*

Bernhard L. Gerber, MD, PhD

Brussels, Belgium

Atherosclerosis is currently no longer considered merely a cholesterol storage disease, but rather a complex process of vascular inflammation (1,2). Indeed, various inflammatory cells and, in particular, monocytes and macrophages play a major role in the development, progression, and rupture of atherosclerotic plaques (3). Atherosclerosis is initiated when blood monocytes and T lymphocytes are attracted by chemokinesis to oxidized apo-B rich lipoproteins in the vessel wall. Expression of vascular cell adhesion molecule-1 and E- and P-selectin by the endothelium allows their adherence and entry into the subendothelial space. Monocytes subsequently

See page 909

differentiate into mature macrophages, ingest the excessive lipoproteins, and become the so-called cholesterol enriched "foam cells." The release of cytokines such as interleukins, Tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and monocyte chemoattractant protein-1 by foam cells and lymphocytes, maintains a state of chronic vascular inflammation, eliciting progression of atherosclerosis. During this process even more monocytes continue to enter the plaque and differentiate into macrophages, while smooth muscle cells and fibroblasts undergo proliferation. This leads to progressive enlargement of the fibro-atheromatous plaque. As atherosclerotic lesions evolve, macrophage foam cells and smooth muscle cells can undergo apoptosis leading to lipid core formation. Plaques with large

lipid cores and thin fibrous caps are considered vulnerable. Ongoing macrophage activation and inflammation leading to necrosis of foam cells is believed to be a major factor in plaque instability. Indeed, inflammatory cytokines and enzymes such as interferon- $\gamma$  secreted by T lymphocytes inhibit production of collagen by smooth muscle cells, while matrix metalloproteinases secreted by macrophages directly degrade and thin the fibrous cap. The release of procoagulant tissue factors by T lymphocytes further increases the thrombogenic potential of the plaque. These factors may lead to endothelial rupture, resulting in exposition of tissue factor to platelets and fibrinogen with subsequent activation of the thrombotic cascade, and acute intravascular thrombus formation. Such acute atherothrombosis is the main mechanism underlying acute coronary syndromes, stroke, and sudden death.

Experimental studies support the view that statins may have unique pleiotropic effects, which may contribute to their exclusive lipid-lowering independent protective clinical efficacy (4). By inhibiting the mevalonate pathway, statins are thought to reduce protein isoprenylation, a process affecting numerous vascular and myocardial signal pathways. For instance, statins favorably affect endothelial nitric oxide synthase (eNOS) gene expression and eNOS coupling in the endothelium. This results in improved nitric oxide bioavailability, improving endothelial dysfunction. Within the atherosclerotic plaque itself, statins reduce reactive oxygen species production by Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase both in the endothelium and the smooth muscle cells. Furthermore, through inhibition of nuclear factor kappa-light-chain-enhancer of activated B cell (NF- $\kappa$ B) activation by TNF- $\alpha$ , statins also reduce vascular small cell monocytes interaction and decrease pro-inflammatory cytokine production such as interleukins, interferon gamma, and monocyte chemoattractant protein 1 expression. Finally, statins down-regulate matrix metalloproteinase activity. All these effects result in strong local anti-inflammatory effects within the plaque, reduction of inflammatory cell infiltration, and plaque stabilization. These marked anti-inflammatory effects of statins can also be demonstrated in vivo, and correlate with reduction of acute events. A particular good example is the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) study (5), where rosuvastatin was shown to reduce event rates in patients with normal low-density lipoprotein cholesterol but high high-sensitivity C-reactive protein (CRP).

To detect vulnerable plaques in high-risk patients and to monitor the effect of drug therapy such as statins on vulnerable plaques in vivo, several noninvasive techniques have been proposed (6). Among these, imaging of vascular inflammation by  $^{18}\text{F}$ -fluorodeoxyglucose positron emission tomography (FDG-PET) is a particularly interesting approach (7). FDG is a glucose analog with a half-life of 110 min, which is taken up by facilitated glucose transporters in competition with glucose into metabolically active cells. It is then phosphorylated to  $^{18}\text{F}$ FDG-6-phosphate by

\*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Division of Cardiology, Department of Cardiovascular Diseases, Cliniques St. Luc and Pôle de Recherche Cardiovasculaire, Institut de Recherche Clinique (IREC), Université Catholique de Louvain, Brussels, Belgium. Dr. Gerber has reported that he has no relationships relevant to the contents of this paper to disclose.

hexokinase, but cannot be metabolized further and thus accumulates within the cell. Clinical studies reported increased FDG uptake in atherosclerotic plaques as compared with normal vessels. Histologically, this FDG uptake is confined mainly to plaque macrophages, but not to surrounding vascular smooth-muscle cells. Indeed macrophages comprise the vast majority of inflammatory cells in human and experimental atherosclerotic plaques, and in the anaerobic environment of the plaque, they preferentially rely on glycolysis for adenosine triphosphate (ATP) production and present increased expression of glucose transporters receptors and hexokinase activity (7). FDG uptake in plaque was shown to correlate significantly with plaque macrophage content, and is therefore thought to be a marker of plaque inflammation. The current methodology for FDG PET imaging of inflammation, involves acquisition of a 10- to 15-min static PET image 2 h after intravenous injection of 10 mCi FDG after overnight fasting. Quantification of FDG uptake in atherosclerotic plaque is performed by measuring the standardized uptake value (SUV) of an artery of interest and of the venous blood pool. Then the vascular target-to-background ratio (TBR) is calculated by dividing the vascular SUV by the venous blood pool SUV. This parameter can be expressed either as maximum or mean TBR for a vessel. This method has been shown to have high sensitivity for detection of vascular inflammation, high inter- and intra-reader reliability, and especially high interstudy reproducibility (8). Another advantage is the simplicity of the method, which is nearly identical to standardized PET protocols widely used for clinical oncology imaging.

Limitations of PET for vascular imaging (9) are, however, its low spatial resolution of 3 to 4 mm requiring coregistration with computed tomography or other techniques to localize the underlying vessel. Moreover, given the small size of atheromatous plaques, imaging with PET is subject to partial volume errors, especially in small vessel such as coronary arteries. A subsequent difficulty for imaging such coronary vessels is the complex motion of the heart. FDG uptake is influenced by dietary status and may be affected by diseases such diabetes mellitus. Vascular signal can also be contaminated by spillover from neighboring muscular or ganglionic structures. Finally, FDG-PET is not a specific tracer of plaque inflammation, as mechanisms other than vascular inflammation may also increase FDG uptake within the atheroma (9). For instance, FDG uptake is dependent on blood flow and could be influenced by vasa-vasorum density in the plaque. It could also increase if regional hypoxia stimulates the glucose utilization rate of monocytes within the plaque. Therefore, more specific nuclear imaging tracers for vascular inflammation, which directly target macrophages or metalloproteinases in the plaque are currently under development (9).

Tawakol et al. (10), in this issue of the *Journal*, compared the effect of low (10 mg) versus high (80 mg) dose atorvastatin on aortic or carotid arteries plaque inflammation in 67 patients by FDG-PET. Patients had prior coronary,

carotid, or peripheral artery disease, diabetes type II, or obesity, were-statin-naive or treated with low-dose statins, and had to have at least 1 “hot” plaque in the aorta or carotid on a baseline FDG-PET. The study evaluated the change of TBR of the most diseased segment of the target vessel at 4 and 12 weeks after statin treatment versus baseline. It demonstrated that both the low- and high-dose of statins reduced FDG-TBR in the target vessel, but that the high-statin dose was more effective in reducing plaque inflammation. Interestingly, but in accordance with other studies, changes of FDG-TBR were not correlated to changes in low-density lipoprotein cholesterol or CRP. This is the first randomized multicenter trial demonstrating such effect of statins on vascular inflammation by FDG-PET. It confirmed findings of an earlier single-center study evaluating simvastatin (11). The main limitation of this study was that there were missing data points, requiring the use of a sophisticated multilinear model for allowing comparison of repeated measurements with missing data. Also the study neither measured other biomarkers of inflammation besides CRP nor followed changes in plaque thickness or composition by techniques such as ultrasound or magnetic resonance imaging.

Besides demonstrating that atorvastatin has anti-inflammatory effects in a dose-dependent response in atherosclerotic patients, the study by Tawakol et al. (10) nicely illustrates the usefulness of FDG-PET to study plaque inflammation and its inflection by drug treatment in vivo. Because of its high costs, it is unlikely that FDG-PET will be widely used to identify high-risk plaques and to monitor treatment response on targeted vessels in individual patients clinically. However, as shown in the study in the present issue PET is attractive to study anti-inflammatory effects of various drugs in experimental trials. Accordingly, it has been used to evaluate effects of cholesterol ester transfer proteins inhibitors (12), p38 mitogen-activated protein kinase inhibitors (13), niacin, ezetimibe, or PPAR- $\gamma$  agonists (14) on plaque inflammation. Using PET to non-invasively study drug effects on plaque inflammation in phase II trials is clearly more attractive and cheaper than invasive techniques such as intravascular ultrasound or optical coherence tomography. Future prospective trials need, however, to establish whether a decrease in plaque inflammation by FDG PET by treatment, translates into a reduced risk of cardiovascular events.

The authors should be congratulated on performing this interesting and well-designed trial, which nicely demonstrates the usefulness of FDG-PET to study drug effect on atherosclerotic plaques in vivo. Further studies employing similar methodology will enhance our understanding on the mode of action and efficacy of new antiatherosclerosis drugs.

---

**Reprint requests and correspondence:** Dr. Bernhard L. Gerber, Cliniques Universitaires St. Luc, Université Catholique de Louvain, Avenue Hippocrate 10/2803, B-1200 Woluwe-Saint-Lambert, Belgium. E-mail: [Bernhard.gerber@uclouvain.be](mailto:Bernhard.gerber@uclouvain.be).

---

## REFERENCES

1. Libby P. Inflammation in atherosclerosis. *Arterioscler Thromb Vasc Biol* 2012;32:2045–51.
2. Spagnoli LG, Bonanno E, Sangiorgi G, Mauriello A. Role of inflammation in atherosclerosis. *J Nucl Med* 2007;48:1800–15.
3. Moore KJ, Tabas I. Macrophages in the pathogenesis of atherosclerosis. *Cell* 2011;145:341–55.
4. Antonopoulos AS, Margaritis M, Lee R, Channon K, Antoniades C. Statins as anti-inflammatory agents in atherogenesis: molecular mechanisms and lessons from the recent clinical trials. *Curr Pharm Des* 2012;18:1519–30.
5. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008;359:2195–207.
6. Vancraeynest D, Pasquet A, Roelants V, Gerber BL, Vanoverschelde JL. Imaging the vulnerable plaque. *J Am Coll Cardiol* 2011;57:1961–79.
7. Joshi F, Rosenbaum D, Bordes S, Rudd JH. Vascular imaging with positron emission tomography. *J Intern Med* 2011;270:99–109.
8. Rudd JH, Myers KS, Bansilal S, et al. Atherosclerosis inflammation imaging with 18F-FDG PET: carotid, iliac, and femoral uptake reproducibility, quantification methods, and recommendations. *J Nucl Med* 2008;49:871–8.
9. Camici PG, Rimoldi OE, Gaemperli O, Libby P. Non-invasive anatomic and functional imaging of vascular inflammation and unstable plaque. *Eur Heart J* 2012;33:1309–17.
10. Tawakol A, Fayad ZA, Mogg R, et al. Intensification of statin therapy results in a rapid reduction in atherosclerotic inflammation: results of a multicenter fluorodeoxyglucose-positron emission tomography/computed tomography feasibility study. *J Am Coll Cardiol* 2013;62:909–17.
11. Tahara N, Kai H, Ishibashi M, et al. Simvastatin attenuates plaque inflammation: evaluation by fluorodeoxyglucose positron emission tomography. *J Am Coll Cardiol* 2006;48:1825–31.
12. Fayad ZA, Mani V, Woodward M, et al. Safety and efficacy of dalcetrapib on atherosclerotic disease using novel non-invasive multimodality imaging (dal-PLAQUE): a randomised clinical trial. *Lancet* 2011;378:1547–59.
13. Elkhawad M, Rudd JH, Sarov-Blat L, et al. Effects of p38 mitogen-activated protein kinase inhibition on vascular and systemic inflammation in patients with atherosclerosis. *J Am Coll Cardiol Img* 2012;5:911–22.
14. Mizoguchi M, Tahara N, Tahara A, et al. Pioglitazone attenuates atherosclerotic plaque inflammation in patients with impaired glucose tolerance or diabetes a prospective, randomized, comparator-controlled study using serial FDG PET/CT imaging study of carotid artery and ascending aorta. *J Am Coll Cardiol Img* 2011;4:1110–8.

---

**Key Words:** atherosclerosis ■ atorvastatin ■ inflammation ■ PET ■ statin.