Published in final edited form as:

Int J Cardiovasc Imaging. 2014 March ; 30(3): 571–582. doi:10.1007/s10554-014-0370-7.

Predictors of change in carotid atherosclerotic plaque inflammation and burden as measured by 18-FDG-PET and MRI, respectively, in the dal-PLAQUE study

Venkatesh Mani,

Translational and Molecular Imaging Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

Department of Radiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Mark Woodward,

George Institute, University of Sydney, Sydney, Australia

Daniel Samber,

Translational and Molecular Imaging Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

Department of Radiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Jan Bucerius,

Translational and Molecular Imaging Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

Department of Radiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Department of Nuclear Medicine, Cardiovascular Research Institute Maastricht (CARIM), Maastricht University Medical Center, Maastricht, The Netherlands

Ahmed Tawakol,

Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA

David Kallend,

F. Hoffmann-La Roche Ltd, Basel, Switzerland

James H. F. Rudd,

Division of Cardiovascular Medicine, University of Cambridge, Cambridge, UK

Markus Abt, and

F. Hoffmann-La Roche Ltd, Basel, Switzerland

Zahi A. Fayad

© Springer Science+Business Media Dordrecht 2014

Correspondence to: Venkatesh Mani, Venkatesh.mani@mssm.edu.

Electronic supplementary material The online version of this article (doi:10.1007/s10554-014-0370-7) contains supplementary material, which is available to authorized users.

Conflict of interest V.M., J.B. and D.S. indicate they have nothing to disclose.

Translational and Molecular Imaging Institute, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

Department of Radiology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Venkatesh Mani: Venkatesh.mani@mssm.edu

Abstract

Baseline predictors of response to treatment of patients with coronary heart disease (CHD) with respect to vascular inflammation and atherosclerotic plaque burden are poorly understood. From post hoc analysis of the dal-PLAQUE study (NCT00655473), 18F-fluorodeoxyglucose-positron emission tomography (18-FDG-PET) imaging and carotid black blood magnetic resonance imaging (MRI) were used to track changes in these vascular parameters. Baseline demographics, imaging, and biomarkers were collected/measured in 130 patients with CHD or CHD risk-equivalents, and imaging follow-up at 6 months (PET) and 24 months (MRI) was performed. Using stepwise linear regression, predictors of change in carotid plaque inflammation by PET [target-to-background ratio (TBR), $n = 92$] and plaque burden by MRI [wall area (WA) and total vessel area (TVA), $n = 89$] were determined. Variables with $p < 0.05$ in multivariable models were considered independently significant. Interleukin-6, systolic blood pressure and standard deviation of wall thickness (WT) at baseline were independently positively associated with 18-FDG uptake (mean of maximum [MeanMax] TBR change over 6 months). Mean of mean TBR, phospholipase A₂, apolipoprotein A-I, and high-sensitivity C-reactive protein at baseline were independently negatively associated with MeanMax TBR change over 6 months. Mean WT and plasminogen activator inhibitor-1 (PAI-1) activity at baseline, and age, were independently associated with change in WA over 24 months. For TVA changes; mean WA and PAI-1 activity at baseline, age, and female gender were independent predictors. These findings may help determine patients most suitable for clinical trials employing plaque inflammation or burden changes as endpoints.

Keywords

Fluorodeoxyglucose-positron emission tomography; Inflammation; Magnetic resonance imaging; Plaque burden

Introduction

Even with advances in modern medicine, atherosclerosis and its inherent consequent metabolic and pathophysiological impact continue to remain among the leading causes of morbidity and mortality in the world [1, 2]. As a result, the identification of both asymptomatic and previously symptomatic individuals who are at risk for future atherothrombotic events is an active area of research in cardiovascular medicine [3].

The development of new drugs that can be used to modulate and treat the atherosclerotic process remains an urgent unmet need [4]. The drug approval process, however, requires the performance of long-term multicenter, randomized, placebo-controlled trials with hard cardiovascular endpoints for evaluation of drug efficacy and safety [5]. Moreover, any new

drug has to be evaluated as a possible adjunct to standard of care, which typically involves the use of statins, thus the sample size requirements for such trials can be very large. Prior to embarking on such long-term trials, it could prove valuable to evaluate the efficacy and safety of newly developed compounds in smaller Phase 2 studies based on surrogate markers for cardiovascular disease/events [6].

Recently, imaging modalities such as 18-fluorodeoxyglucose positron emission tomography (18-FDG-PET) [7–11] and magnetic resonance imaging (MRI) [12, 13] have gained prominence as methodologies suitable for the *in vivo* measurement of plaque inflammation and burden of atherosclerotic disease. Notably, these techniques were used to evaluate the effect of therapeutic intervention on plaque burden in several recent clinical studies [14, 15]. While the short term reproducibility (typically over 1–2 weeks) of these imaging modalities is well established [16, 17], natural changes in these parameters over the long term are poorly understood. Plaque inflammation, for example, is considered to be a transient phenomenon, whereas indices of plaque burden are generally considered to increase with time in cases where no intervention is provided. Importantly, the risk factors that influence changes in these imaging parameters over time are also not well characterized.

The dal-PLAQUE study—a multicenter, placebo-controlled trial of the cholesteryl ester transfer protein (CETP) modulator dalcetrapib—assessed structural and inflammatory indices of atherosclerosis as primary endpoints [6, 14]. Patients included in this study had previously received statins and had low low-density lipoprotein cholesterol (LDL-C) and high sensitivity C-reactive protein (hs-CRP) levels. Although dal-PLAQUE showed no adverse effect of high-density lipoprotein (HDL)-raising on vascular function in these patients, failure of the dal-OUTCOMES trial (among others) to show clinical benefit from HDL-raising [18–20], and a poor understanding of natural changes in imaging modalities, led us to consider that potential clinical benefit might be precluded by specific metabolic characteristics.

As such, the dal-PLAQUE study presented us with an ideal opportunity to examine the role of baseline characteristics of the patients on changes in plaque inflammatory status and plaque burden over a relatively long period of time: 6 months for PET-derived plaque inflammation and 24 months for MRI-derived plaque burden. 18F-fluor-odeoxyglucose-positron emission tomography (18-FDG-PET) imaging and carotid black blood magnetic resonance imaging (MRI) can be used to evaluate and monitor serial changes in vascular inflammation and atherosclerotic plaque burden, respectively, but the role of baseline variables in predicting changes in these imaging metrics in patients with coronary heart disease is poorly understood. In this study, we try to elucidate the role of baseline variables including patient demographics, biomarkers and imaging markers on the changes in plaque inflammation and burden over the long term.

Methods

The design and primary findings of the dal-PLAQUE study (ClinicalTrials.gov identifier: NCT00655473) have been published previously [6, 14]. In brief, 130 patients with coronary heart disease (CHD) or CHD risk equivalents from 11 centers in the United States and

Canada were randomized to receive 24 months' double-blind treatment with dalcetrapib 600 mg/day (n = 64) or placebo (n = 66), on a background of standard care (Fig. 1). Subjects with an average baseline mean maximal arterial wall target-to-background ratio (TBR) 1.6 were eligible for randomization. Non-invasive PET and high-resolution black-blood MRI techniques were used to evaluate inflammatory status and vessel wall structure, respectively.

PET/CT imaging

The PET acquisition and analysis methodology has been previously published [6, 14]. Patients were imaged after an overnight fast on a PET/computed tomography (CT) scanner 90 min after injection of 10 mCi of 18-FDG. A low-dose CT scan (140 kV, 80 mA, and 4.25-mm slice thickness) was used to correct for attenuation and for anatomical co-registration purposes. Images from one bed position in 3D mode, using a 128 × 128 pixel matrix for 10 min, were acquired for carotid evaluation, and two bed positions in 2D mode for 10 min each were acquired for aortic evaluation.

Arterial FDG uptake was quantified by manually delineating a region of interest (ROI) on co-registered transaxial PET/CT images. A circular ROI was drawn to encompass the vessel wall on each contiguous axial segment. Next, the maximum arterial standardized uptake value (SUV) was determined; SUV being defined as the decay-corrected tissue concentration of FDG in kBq/mL, adjusted for the injected FDG dose and the body weight of the patient. Various PET indices are then derived from the ROIs placed on the vessel. Each axial segment provides two measures: a mean and a maximum value for FDG uptake within that segment. Venous uptake was used for background correction, with the ratio of segment to the background yielding the target to background ratio (TBR). The mean of mean (MeanMean) TBR was the average of mean TBR values from each artery while the mean of maximum (MeanMax) TBR was the average of maximal TBR values from each artery. All analyses described relate to MeanMax TBR values at baseline and change in this parameter over 6 months and, accordingly indeed, the vessel with the highest MeanMax TBR at baseline was assigned as the index vessel. The most disease segment (MDS) was a further PET index derived by averaging the three highest contiguous segments centered at the segment with the highest maximum TBR.

All PET images were first subjectively evaluated for image quality by an expert using a three-point scale. (1, poor—rejected; 2, adequate—accepted; and 3, good—accepted). Only images of acceptable or higher quality were used in the analysis. Examples of typical images are provided in Supplementary materials.

MRI

The imaging acquisition methodologies used in this study have been previously described [6, 14]. Briefly, carotid arteries and abdominal aorta were imaged with patients in a head-first supine position at baseline and 24 months follow-up during the treatment period. After obtaining scout images, 2D multi-contrast (proton density-weighted, T1-weighted and T2-weighted) dark-blood turbo spin echo images were acquired to quantify vessel wall metrics for both the descending abdominal aorta and the common carotid arteries [21]. Carotid

bifurcations were further localized using phase contrast images, and a time-of-flight acquisition was acquired as an aid towards identifying lumen contours.

All MRI images were evaluated as described above for PET images but using a five-point scale (1—poor, 5—best) based upon four metrics (overall image quality, vessel wall delineation, flow suppression efficiency, and presence of artefacts). Only images with quality for all four metrics were used in the analysis.

MRI analysis has also been described previously [6, 14]. Vessel wall boundaries and outer and inner walls of the carotid arteries and abdominal aorta were manually traced to derive MRI metrics of plaque burden; including lumen area, vessel wall area (WA), total vessel area (TVA), wall thickness, standard deviation (SD) of wall thickness, and a normalized wall index (WA/TVA ratio) [17, 22].

Statistical analysis

Linear regression—All patients from the dal-PLAQUE study with MeanMax TBR data at baseline and 6 months were included in the analysis of PET/CT images, and those with WA and TVA data at baseline and 24 months were included for MRI. Data from 5 subjects from 110 (<5 %) were excluded from the analysis due to poor image quality.

PET/CT: A stepwise multiple linear regression analysis was used to determine predictors of absolute change from baseline in MeanMax TBR over 6 months using all available data and all baseline variables as candidates for the model. This analysis was not performed for MDS TBR, as absolute change in MeanMax TBR was the a priori determined primary endpoint in the dal-PLAQUE study. According to the largest improvement, variables with $p < 0.15$ were entered to the model. Only those variables with $p < 0.1$ were retained. Due to missing values in some covariates, only patients with data on all covariates were used for the selected variables. Therefore the finally selected model was refitted again using the selected variables only. Final results were obtained from this model by again eliminating variables until $p < 0.05$ was attained for all variables. The final model included 92 patients who had data for all remaining variables.

MRI: All patients from dal-PLAQUE with 24-month MRI follow-up data were included in the analysis. To assess the major determinants of change in atherosclerotic plaque burden, a procedure similar to that described above for the PET analysis was employed. Separate analyses were performed for absolute change from baseline for TVA as well as WA. Thus, in the current analysis, TVA and WA were each used separately as dependent variables in the regression analysis, with input baseline demographics, biomarkers and imaging parameters from the dal-PLAQUE study used as independent variables. The final model comprised 89 patients who had data for all remaining variables.

In the dal-PLAQUE study, MRI-derived change in TVA was significantly reduced after 24 months in patients who received dalcetrapib, compared with placebo. This was accompanied by a non-significant reduction in WA. To account for any drug-related effects, randomized treatment was forced into the model for both the PET/CT and MRI regression analysis.

All statistical analyses were performed using PROC GLMSELECT and PROC MIXED in SAS (Version 9.2, SAS Institute Inc., Cary, NC, USA).

Results

Baseline measures for demographic, biomarker and imaging variables from the dal-PLAQUE study and used in the PET/CT and MRI regression analyses are presented in Table 1. Eighty-seven percent of patients had previously used a statin, mean LDL-C level was 74.5 mg/dL, and median hsCRP was 1.4 mg/L.

18-FDG-PET/CT-derived inflammation

The SD of wall thickness, interleukin (IL)-6, and systolic blood pressure at baseline were independently positively associated with increased 18-FDG-PET/CT uptake defined as MeanMax TBR change over 6 months (Table 2; Fig. 2). Based on all available data, dalcetrapib treatment was not associated with MeanMax TBR change over 6 months ($p = 0.9872$). MeanMean TBR, phospholipase A₂ (PLA₂), apolipoprotein (Apo) A-I, and hsCRP at baseline were independently negatively associated with MeanMax TBR change over 6 months (Table 2; Fig. 2). No significant treatment interaction was evident for any of the above variables.

MRI-derived plaque burden

Mean wall thickness and plasminogen activator inhibitor-1 (PAI-1) activity at baseline, as well as age, were independently associated (negative, positive, positive, respectively) with change in WA over 24 months (Table 3; Fig. 3). In regard to TVA, mean WA and PAI-1 activity at baseline, as well as age and female gender, were significant independent predictors of changes in TVA. Although, relative to placebo, treatment with dalcetrapib 600 mg for 24 months was associated with a significant decrease in TVA (Table 3; Fig. 3) and a trend for decreased WA, as above, there was no significant treatment interaction.

Discussion

In this post hoc analysis of dal-PLAQUE data, we attempted to look at baseline biomarkers and imaging markers of cardiovascular risk that were associated with progression of atherosclerotic plaque inflammation as defined by 18-FDG-PET, and atherosclerotic plaque burden as measured by dark-blood MRI-derived metrics. To our knowledge, this is among only a few studies that look at predictors of change in plaque inflammation and burden rather than just associations with these metrics. The findings from this study could provide additional insight towards the design of future clinical trials that employ imaging endpoints in identifying variables that could potentially confound the natural course of imaging markers of plaque inflammation and burden.

Markers of plaque inflammation progression

Previous studies, albeit in single centers, have shown several factors to be associated with increased plaque inflammation. In a study in 82 patients with coronary artery disease, Bucerius et al. [23] showed smoking and hypertension to be associated with increased *TBR*

values. In this study, and in agreement with previous reported findings, we have shown higher systolic blood pressure to be associated with increased progression of 18-FDG-PET-defined inflammation. An association with smoking status was not observed in the current study possibly due to differences in our study population compared with that of Bucerius et al. [23]. For example, in the current study, 26 % of subjects (12 % control group; 14 % dalcetrapib group) were current smokers, whereas Bucerius et al. reported 46 % of the subjects as prior or current smokers. Moreover, these authors also reported that body mass index (BMI) was significantly associated with PET-based inflammation. However, this relationship was not observed in our dal-PLAQUE post hoc analysis, despite the mean BMI being higher in the dal-PLAQUE cohort (29.7 vs. 27.8 kg/m²). The observed discrepancy might be due in part to the larger sample size used in our study, perhaps representing a relatively robust dataset, or that Bucerius et al. sub-divided BMI into three groups used as categorical variables, whereas we input BMI into the regression model as a continuous variable; this is particularly significant as continuous variable analyses reported in previous studies, similarly, did not show significant associations between BMI and PET-based inflammation. Furthermore, this dal-PLAQUE post hoc analysis evaluated changes in plaque inflammation over a 6-month period rather than an association with plaque inflammation at the time of data acquisition per se.

The SD of wall thickness on MRI, a measure of plaque eccentricity at baseline, was found to be independently associated with increases in MeanMax TBR over 6 months; findings consistent with previous studies where SD of wall thickness has been shown to be associated with prior cardiovascular events [22]. Increased IL-6 at baseline was associated with increased progression of inflammation. This is not unexpected, given previous reports that IL-6 can be proatherogenic through the up-regulation of macrophage scavenger receptors [24].

Association of MeanMean TBR and hsCRP at baseline and with progression of inflammation—

In this study we have shown also that a higher baseline MeanMean TBR was associated with a lower increase (decrease) of plaque inflammation as defined by FDG-PET uptake. While this could indicate a “regression to the mean effect”, it could also indicate that the study participants were already at a high-inflammatory status at baseline i.e., a MeanMax TBR > 1.6 was a pre-requisite for enrolment, thus, any further increase in vessel wall inflammatory status over the course of the study was not possible or apparent. It is also possible that hsCRP measures may be more indicative of global inflammation within an individual and not truly reflective of plaque or local vascular inflammation as measured by 18-FDG-PET. Collectively, these caveats may help explain why the observed increase in hsCRP was inversely associated with progression of plaque inflammation, i.e., an unexpected finding in this study.

Association between ApoA-I, PLA₂ and plaque inflammation—

The atheroprotective effects of ApoA-I are well established [25–27], and the finding in our study that increased ApoA-I at baseline was inversely associated with increases in plaque inflammation was consistent with this central tenet. However, plasma PLA₂ level was observed to be inversely associated with plaque inflammatory changes, i.e., contrary to

expectations given that previously reported studies examining PLA₂-mediated increases in plaque inflammation showed that PLA₂ inhibition can reduce inflammation [28, 29].

Markers of progression of plaque burden

Mean wall thickness and PAI-1 activity at baseline, as well as age, were found to be independently associated with change in WA over 24 months while, for changes in TVA, mean WA and PAI-1 activity at baseline, and age and gender, were significant independent predictors. Several studies have established age as the strongest risk factor for atherosclerosis progression and this association was evident from our analysis, with increased age being one of the strongest independent predictors of progression of plaque burden, measured both as change in WA and TVA.

There is a strong body of published evidence to support high levels of PAI-1 as being associated with cardiovascular risk factors in both at risk and healthy individuals [30, 31]. This would indicate that PAI-1 activity increases should be associated with decreases in cardiovascular risk, and the data in our study show this effect; with increases in PAI-1 activity being associated with reduced plaque progression as defined by TVA and WA changes on MRI over 2 years.

Increased plaque burden at baseline; wall thickness (for changes in WA) and WA (for changes in TVA) were associated with less progression over 2 years. As alluded to earlier in regard to baseline inflammatory status, such an inverse relationship might simply mirror an already significantly advanced plaque burden at baseline that did not show any notable further increase over the 2-year follow-up period. Notably, both female gender and dalcetrapib treatment were significantly and negatively associated with plaque progression indicating that potentially cardioprotective effects might be conferred by gender and by dalcetrapib.

Relevance of current results

Our findings indicate that knowledge of the baseline characteristics of patients can be utilized to pre-select a suitable study population for drug trials intended to employ imaging as an endpoint. This means that data will show only minimal confounding by patient history and, thus, be subjected to minimal bias only. For example, in avoiding enrolment of individuals at extreme ranges for baseline plaque eccentricity, IL-6, systolic blood pressure, PLA₂ level and inflammatory status (hsCRP), investigators involved in future clinical trials will have greater confidence that any observed effect on plaque inflammation is due to the novel study treatment under examination rather than variances in baseline characteristics of the study cohort. Moreover, such an approach may aid reduction in sample size requirements for future studies. Similarly, when using plaque burden measures by MRI as an end-point, it may be possible to establish a relatively restricted range for PAI-1 activity at baseline/ randomization while ensuring enrolment eligibility criteria are maintained.

Limitations

A key limitation of this study was small sample size, particularly in relation to the number of variables considered as potential predictors. However, only a few studies have been

performed to identify such potential predictors of treatment efficacy, particularly using combined complementary methodologies, hence we judge our results add importantly to the evidence base for the innovative technologies used. Future meta-analyses will be required to confirm our findings.

Another potential limitation is that the data for this post hoc analysis were obtained from a trial of a drug developed to modulate CETP activity and thus raise plasma levels of HDL cholesterol, an approach that could potentially and significantly skew the findings. To help control for this, dalcetrapib treatment was forced into the regression model at all stages. The alternative to using this approach was to only analyze the control group, but this would have approximately halved the sample size, not only reducing power but also rendering modeling increasingly subject to effects from extreme values. As this was a multicenter study, with data obtained from several different scanners from multiple vendors, the variability of imaging markers could have been increased compared to a single-center study, further reducing power. However, SDs of the data for the imaging markers used in this study were comparable to those from several previous single center studies [32, 33]. Although not perhaps a limitation, focus here was placed on absolute change in TBR i.e., the dal-PLAQUE trial primary endpoint, not percent change and significant differences in findings were not anticipated regardless of either metric used.

While there could be an effect on the findings from quantification of the imaging metrics per se, the results obtained are considered valid as only images of adequate quality were used for the analysis described earlier (Methods, examples are provided in Supplementary materials).

Conclusions

In this post hoc analysis of dal-PLAQUE data, using linear regression analysis, we have identified several baseline variables (demographics, biomarkers, and imaging metrics) that are associated with change in atherosclerotic inflammation as measured by 18-FDG-PET, and plaque burden as measured by MRI.

Standard deviation of wall thickness, IL-6, and systolic blood pressure were positively associated with MeanMax TBR changes over 6 months, whereas MeanMean TBR, PLA₂, ApoA-I and inflammatory status (hsCRP) at baseline were negatively associated with MeanMax TBR changes over 6 months. Age and PAI-1 activity were independently associated with changes in both wall and TVA over 24 months.

The identification of predictive markers may assist selection of patients most suitable for clinical trials evaluating plaque inflammatory status on 18-FDG-PET-CT or plaque burden changes on MRI, as an endpoint. This should increase trial efficiency, enabling enrichment of samples and possible reduction in the sample size required for adequate power.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank Michael E. Farkouh and Valentin Fuster for their review and feedback of the manuscript. This study was funded by F. Hoffmann-La Roche Ltd. Editorial assistance was provided by Prime Healthcare during the preparation of this report, and funded by F. Hoffmann-La Roche Ltd. All opinions expressed are those of the authors.

M.W. discloses that he has received honoraria from Roche. A.T. discloses that he has received honoraria from Roche, BMS and Novartis, and research grants from Merck, BMS, Genentech, GSK and VBL. D.K. was an employee of F. Hoffman-La Roche Ltd at the time the study was performed. M.A. is an employee of F.Hoffman-La Roche Ltd and receives share options. J.H.F.R. discloses that he has received honoraria from Roche and is part-supported by the National Institute for Health Research Cambridge Biomedical Research Centre. Z.A.F. discloses that he has received research grants from Roche, Glaxo-SmithKline, Merck, VBL Therapeutics, Novartis, Bristol-Myers Squibb, and Via Pharmaceuticals and honoraria from Roche.

References

1. Lobatto ME, Fuster V, Fayad ZA, Mulder WJ. Perspectives and opportunities for nanomedicine in the management of atherosclerosis. *Nat Rev Drug Discov.* 2011; 10:835–852. [PubMed: 22015921]
2. Underhill HR, Hatsukami TS, Fayad ZA, Fuster V, Yuan C. MRI of carotid atherosclerosis: clinical implications and future directions. *Nat Rev Cardiol.* 2010; 7:165–173. [PubMed: 20101259]
3. Sekikawa A, Curb JD, Edmundowicz D, Okamura T, Choo J, Fujiyoshi A, Masaki K, Miura K, Kuller LH, Shin C, Ueshima H. Coronary artery calcification by computed tomography in epidemiologic research and cardiovascular disease prevention. *J Epidemiol.* 2012; 22:188–198. [PubMed: 22485011]
4. Parakevas KI, Wierzbicki AS, Mikhailidis DP. Statins and noncardiac vascular disease. *Curr Opin Cardiol.* 2012; 27:392–397. [PubMed: 22525327]
5. Fryburg DA, Vassileva MT. Atherosclerosis drug development in jeopardy: the need for predictive biomarkers of treatment response. *Sci Transl Med.* 2011; 3(72):1–5.
6. Fayad ZA, Mani V, Woodward M, Kallend D, Bansilal S, Pozza J, Burgess T, Fuster V, Rudd JH, Tawakol A, Farkouh ME. Rationale and design of dal-PLAQUE: a study assessing efficacy and safety of dalcetapib on progression or regression of atherosclerosis using magnetic resonance imaging and 18F-fluorode-oxyglucose positron emission tomography/computed tomography. *Am Heart J.* 2011; 162(2):214–221. [PubMed: 21835280]
7. Rudd JH, Warburton EA, Fryer TD, Jones HA, Clark JC, Antoun N, Johnström P, Davenport AP, Kirkpatrick PJ, Arch BN, Pickard JD, Weissberg PL. Imaging atherosclerotic plaque inflammation with [18F]-fluorodeoxyglucose positron emission tomography. *Circulation.* 2002; 105:2708–2711. [PubMed: 12057982]
8. James OG, Christensen JD, Wong TZ, Borges-Neto S, Kowek LM. Utility of FDG PET/CT in inflammatory cardiovascular disease. *Radiographics.* 2011; 31:1271–1286. [PubMed: 21918044]
9. Mizoguchi M, Tahara N, Tahara A, Nitta Y, Kodama N, Oba T, Mawatari K, Yasukawa H, Kaida H, Ishibashi M, Hayabuchi N, Harada H, Ikeda H, Yamagishi S, Imaizumi T. Pioglitaz-one 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. *JACC Car-diovasc Imaging.* 2011; 4:1110–1118.
10. Ogawa M, Nakamura S, Saito Y, Kosugi M, Magata Y. What can be seen by 18F-FDG PET in atherosclerosis imaging? The effect of foam cell formation on 18F-FDG uptake to mac-rophages in vitro. *J Nucl Med.* 2012; 53:55–58. [PubMed: 22128324]
11. Rosenbaum D, Millon A, Fayad ZA. Molecular imaging in atherosclerosis: FDG PET. *Curr Atheroscler Rep.* 2012; 14:429–437. [PubMed: 22872371]
12. Tardif JC, Lesage F, Harel F, Romeo P, Pressacco J. Imaging biomarkers in atherosclerosis trials. *Circ Cardiovasc Imaging.* 2011; 4:319–333. [PubMed: 21586743]
13. Corti R, Fuster V. Imaging of atherosclerosis: magnetic resonance imaging. *Eur Heart J.* 2011; 32(14):1709–1719. [PubMed: 21508002]
14. Fayad ZA, Mani V, Woodward M, Kallend D, Abt M, Burgess T, Fuster V, Ballantyne CM, Stein EA, Tardif JC, Rudd JH, Farkouh ME, Tawakol A. dal-PLAQUE Investigators. Safety and

- efficacy of dalcetrapib on atherosclerotic disease using novel non-invasive multimodality imaging (dal-PLAQUE): a randomised clinical trial. *Lancet*. 2011; 378:1547–1559. [PubMed: 21908036]
15. Fayad ZA, Mani V, Fuster V. The time has come for clinical cardiovascular trials with plaque characterization as an endpoint. *Eur Heart J*. 2012; 33:160–161. [PubMed: 21875863]
 16. Rudd JH, Myers KS, Bansilal S, Machac J, Pinto CA, Tong C, Rafique A, Hargeaves R, Farkouh M, Fuster V, Fayad ZA. Atherosclerosis inflammation imaging with 18F-FDG PET: carotid, iliac, and femoral uptake reproducibility, quantification methods, and recommendations. *J Nucl Med*. 2008; 49:871–878. [PubMed: 18483100]
 17. El Aidi H, Mani V, Weinshelbaum KB, Aguiar SH, Taniguchi H, Postley JE, Samber DD, Cohen EI, Stern J, van der Geest RJ, Reiber JH, Woodward M, Fuster V, Gidding SS, Fayad ZA. Cross-sectional, prospective study of MRI reproducibility in the assessment of plaque burden of the carotid arteries and aorta. *Nat Clin Pract Cardiovasc Med*. 2009; 6:219–228. [PubMed: 19174763]
 18. Boden WE, Probstfield JL, Anderson T, Chaitman BR, Desvignes-Nickens P, Koprowicz K, McBride R, Teo K, Weintraub W. Investigators AIM-HIGH. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *N Engl J Med*. 2011; 365:2255–2267. [PubMed: 22085343]
 19. Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesäniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M. FIELD study investigators. Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. *Lancet*. 2005; 366:1849–1861. [PubMed: 16310551]
 20. Schwartz GG, Olsson AG, Abt M, Ballantyne CM, Barter PJ, Brumm J, Chaitman BR, Holme IM, Kallend D, Leiter LA, Leitersdorf E, McMurray JJ, Mundl H, Nicholls SJ, Shah PK, Tardif JC, Wright RS. dal-OUTCOMES Investigators. Effects of dalcetrapib in patients with a recent acute coronary syndrome. *N Engl J Med*. 2012; 367:2089–2099. [PubMed: 23126252]
 21. Hayashi K, Mani V, Nemade A, Aguiar S, Postley JE, Fuster V, Fayad ZA. Variations in atherosclerosis and remodeling patterns in aorta and carotids. *J Cardiovasc Magn Reson*. 2010; 12:10. [PubMed: 20205722]
 22. Mani V, Muntner P, Gidding SS, Aguiar SH, El Aidi H, Weinshelbaum KB, Taniguchi H, van der Geest R, Reiber JH, Bansilal S, Farkouh M, Fuster V, Postley JE, Woodward M, Fayad ZA. Cardiovascular magnetic resonance parameters of atherosclerotic plaque burden improve discrimination of prior major adverse cardiovascular events. *J Cardiovasc Magn Reson*. 2009; 11:10. [PubMed: 19393089]
 23. Bucerius J, Duivenvoorden R, Mani V, Moncrieff C, Rudd JH, Calcagno C, Machac J, Fuster V, Farkouh ME, Fayad ZA. Prevalence and risk factors of carotid vessel wall inflammation in coronary artery disease patients: FDG-PET and CT imaging study. *JACC Cardiovasc Imaging*. 2011; 4:1195–1205. [PubMed: 22093271]
 24. Hashizume M, Mihara M. Atherogenic effects of TNF- α and IL-6 via up-regulation of scavenger receptors. *Cytokine*. 2012; 58:424–430. [PubMed: 22436638]
 25. Reimers GJ, Jackson CL, Rickards J, Chan PY, Cohn JS, Rye KA, Barter PJ, Rodgers KJ. Inhibition of rupture of established atherosclerotic plaques by treatment with apolipo-protein A-I. *Cardiovasc Res*. 2011; 91:37–44. [PubMed: 21354994]
 26. Morgantini C, Imaizumi S, Grijalva V, Navab M, Fogelman AM, Reddy ST. Apolipoprotein A-I mimetic peptides prevent atherosclerosis development and reduce plaque inflammation in a murine model of diabetes. *Diabetes*. 2010; 59:3223–3228. [PubMed: 20826564]
 27. Cimmino G, Ibanez B, Vilahur G, Speidl WS, Fuster V, Badimon L, Badimon JJ. Up-regulation of reverse cholesterol transport key players and rescue from global inflammation by ApoA-I(Milano). *J Cell Mol Med*. 2009; 13:3226–3235. [PubMed: 19120689]
 28. Hu MM, Zhang J, Wang WY, Wu WY, Ma YL, Chen WH, Wang YP. The inhibition of lipoprotein-associated phospholipase A2 exerts beneficial effects against atherosclerosis in LDLR-deficient mice. *Acta Pharmacol Sin*. 2011; 32:1253–1258. [PubMed: 21970837]
 29. Gonçalves I, Edsfieldt A, Ko NY, Grufman H, Berg K, Björkbacka H, Nitulescu M, Persson A, Nilsson M, Prehn C, Adamski J, Nilsson J. Evidence supporting a key role of Lp-PLA2-generated lysophosphatidylcholine in human atherosclerotic plaque inflammation. *Arterioscler Thromb Vasc Biol*. 2012; 32:1505–1512. [PubMed: 22499993]

30. Agirbasli M. Pivotal role of plasminogen-activator inhibitor 1 in vascular disease. *Int J Clin Pract*. 2005; 59:102–106. [PubMed: 15707473]
31. Raiko JR, Oikonen M, Wendelin-Saarenhovi M, Siitonen N, Kähönen M, Lehtimäki T, Viikari J, Jula A, Loo BM, Huupponen R, Saarikoski L, Juonala M, Raitakari OT. Plasminogen activator inhibitor-1 associates with cardiovascular risk factors in healthy young adults in the Cardiovascular Risk in Young Finns Study. *Atherosclerosis*. 2012; 224:208–212. [PubMed: 22840426]
32. Mani V, Aguiar SH, Itskovich VV, Weinshelbaum KB, Postley JE, Wasenda EJ, Aguinaldo JG, Samber DD, Fayad ZA. Carotid black blood MRI burden of atherosclerotic disease assessment correlates with ultrasound intima-media thickness. *J Cardiovasc Magn Reson*. 2006; 8:529–534. [PubMed: 16755842]
33. Bucarius J, Mani V, Moncrieff C, Rudd JH, Machac J, Fuster V, Farkouh ME, Fayad ZA. Impact of noninsulin-dependent type 2 diabetes on carotid wall 18F-fluorodeoxy-glucose positron emission tomography uptake. *J Am Coll Cardiol*. 2012; 59:2080–2088. [PubMed: 22651864]

Fig. 1.
Study design. Reproduced from Fayad et al. [6] (with permission)

Fig. 2.
Significant associations with MeanMax TBR change over 6 months by 18-FDG-PET/CT.
Lines plotted are based on linear regression analysis. TBR target to background ratio

Fig. 3. Baseline variables associated with change in carotid **a** WA and **b** TVA, over 24 months by MRI. Lines plotted are based on linear regression analysis. *PAI-1* plasminogen activator inhibitor-1

Table 1

Baseline characteristics (dal-PLAQUE study)

	Overall (n = 130)	Dalcetrapib (n = 64)	Placebo (n = 66)	<i>p</i> [†]
<i>Demographics</i>				
Age (years)	63.6 (8.1)	62.6 (8.2)	64.6 (7.8)	0.157
Male gender	106 (82 %)	51 (80 %)	55 (83 %)	na
BMI (kg/m ²)	29.7 (5.5)	29.6 (4.8)	29.8 (6.2)	0.895
White race	120 (92 %)	58 (91 %)	62 (94 %)	na
History of CHD	111 (87 %)	57 (89 %)	54 (82 %)	0.357
Symptomatic CAD	10 (8 %)	5 (8 %)	5 (8 %)	0.781
Hypertension	95 (74 %)	47 (73 %)	48 (73 %)	0.915
Type 2 diabetes	39 (30 %)	19 (30 %)	20 (30 %)	0.909
Abdominal aortic aneurysm	5 (4 %)	3 (5 %)	2 (3 %)	0.972
PAD	16 (12 %)	6 (9 %)	10 (15 %)	0.462
Present smoker	17 (13 %)	9 (14 %)	8 (12 %)	0.946
Statin use	113 (87 %)	52 (81 %)	61 (92 %)	0.103
<i>Imaging parameters</i>				
18-FDG-PET/CT (inflammation, aortic and carotid) ^a				
MeanMean TBR	1.9 (0.36)	1.8 (0.37)	1.9 (0.35)	0.063
MeanMax TBR	2.6 (0.6)	2.5 (0.62)	2.6 (0.64)	0.447
MRI (plaque burden, mean carotid) ^b				
TVA (mm ²)	61.5 (15.4)	62.8 (17.8)	60.2 (12.9)	0.381
WA (mm ²)	29.8 (9.1)	30.0 (9.3)	29.5 (8.9)	0.761
Wall thickness (mm)	1.2 (0.25)	1.2 (0.22)	1.2 (0.29)	0.726
Normalized wall index (%)	47.6 (6.42)	47.1 (5.93)	48.1 (6.91)	0.408
<i>Biomarkers</i>				
TC (mg/dL)	145.6 (27.5)	143.7 (26.7)	147.9 (28.1)	0.384
LDL-C (mg/dL)	74.5 (20.9)	73.7 (22.3)	74.6 (19.8)	0.808
HDL-C (mg/dL)	44.0 (13.4)	42.4 (11.5)	46.3 (15.1)	0.100
TG, mg/dL (median, IQR)	124.5 (88.0–165.0)	123.5 (84.5–169.5)	128.0 (93.0–159.0)	0.663
SBP (mmHg)	121.4 (15.4)	119.5 (14.5)	123.1 (16.1)	0.185
DBP (mmHg)	72.3 (8.9)	72.8 (9.2)	71.9 (8.6)	0.567
HbA1c (%)	6.2 (0.8)	6.2 (0.8)	6.2 (0.9)	0.725
ApoA-I (mg/dL)	142.9 (26.7)	140.8 (23.2)	144.9 (30.1)	0.394
Insulin sensitivity, HOMA_IR	32.7 (42.1)	33.5 (49.5)	31.9 (34.6)	0.830
eGFR (ml/min/1.73 m ²)	76.4 (12.9)	78.3 (13.4)	74.5 (12.3)	0.096
hsCRP, mg/l (median, IQR)	1.4 (0.6–3.2)	1.4 (0.6–3.7)	1.4 (0.8–2.8)	0.750
IL-6 (pg/mL)	3.8 (4.9)	3.7 (2.9)	3.9 (6.3)	0.837
sP-selectin (ng/mL)	73.2 (22.6)	74.6 (21.1)	71.9 (24.1)	0.492
sE-selectin (ng/mL)	41.3 (15.7)	41.1 (14.8)	41.5 (16.6)	0.889
sICAM (ng/mL)	238.5 (67.1)	239.4 (61.2)	237.6 (72.9)	0.884

	Overall (n = 130)	Dalcetrapib (n = 64)	Placebo (n = 66)	$p^{\dagger}$
sVCAM (ng/mL)	821.2 (223.9)	784.7 (175.6)	857.1 (259.3)	0.068
PLA ₂ (ng/mL)	194.3 (42.8)	199.3 (44.8)	189.4 (40.6)	0.194
MMP-3 (ng/mL)	19.3 (10.9)	18.5 (8.6)	20.1 (12.9)	0.424
MMP-9 (ng/mL)	555.4 (312.2)	544.7 (301.6)	565.9 (324.3)	0.703
MPO (pmol/L)	1,059.6 (4,474.8)	675.1 (468.0)	1,438.1 (6,288.0)	0.339
TPA (ng/mL)	7.0 (9.5)	6.6 (5.8)	7.5 (12.1)	0.574
PAI-1 activity (IU/mL)	15.9 (8.6)	16.7 (8.7)	15.1 (8.6)	0.319
PAI-1 antigen (ng/mL)	62.8 (43.8)	65.5 (46.5)	60.2 (41.1)	0.493

Values are n (%) or mean (SD), unless otherwise stated. Conversion from mg/dL to mmol/L: for TC, LDL-C, HDL multiply by 0.0259, for TG multiply by 0.0113

18-FDG-PET 18F-fluorodeoxyglucose-positron emission tomography/computed tomography, *ApoA-I* apolipoprotein A-I, *BMI* body mass index, *CAD* coronary artery disease, *CHD* coronary heart disease, *CT* computed tomography, *DBP* diastolic blood pressure, *eGFR* estimated glomerular filtration rate, *HbA1c* glycated hemoglobin, *HDL-C* high-density lipoprotein cholesterol, *hsCRP* high sensitivity C-reactive protein, *HOMA-IR* homeostasis model assessment-estimated insulin resistance, *IL* interleukin, *IQR* interquartile range, *LDL-C* low-density lipoprotein cholesterol, *MeanMax* mean of maximum, *MeanMean* mean of mean, *MMP* matrix metalloproteinase, *MPO* myeloperoxidase, *MRI* magnetic resonance imaging, *na* not applicable, *PAD* peripheral artery disease, *PAI-1* plasminogen activator inhibitor 1, *PLA₂* phospholipase A₂*SBP* systolic blood pressure, *SD* standard deviation, *sICAM* soluble intercellular adhesion molecule 1, *sVCAM* soluble vascular adhesion molecule 1, *sP* soluble platelet, *sE* soluble endothelial, *TBR* target to background ratio, *TC* total cholesterol, *TG* triglyceride, *TPA* tissue plasminogen activator, *TVA* total vessel area, *WA* wall area

† *P* values based on two-sample *t* test except 'History of' parameters; χ^2 test with continuity correction

^a Total number of patients with MRI vessel parameter measurements was 56 each for placebo and dalcetrapib. Includes all patients with measurements available, one patient with an index vessel of aorta had inadequate scans at baseline for analysis

^b Total number of patients with MRI vessel parameter measurements was 56 for placebo and 58 for dalcetrapib. Includes all patients with measurements available

Table 2

Baseline variables associated ($p < 0.05$) with MeanMax TBR change over 6 months by 18-FDG-PET/CT, plus randomized treatment

Variable	Coefficient	95 % CI	<i>p</i> value ^a
Dalcetrapib treatment	−0.002	−0.207, 0.204	0.99
Significant positive associations			
SD of wall thickness (mm)	1.101	0.197, 2.004	0.02
IL-6 (pg/mL)	0.033	0.003, 0.062	0.03
SBP (mmHg)	0.008	0.001, 0.015	0.03
Significant negative associations			
MeanMax TBR (baseline)	−0.893	−1.150, −0.635	<0.0001
PLA ₂ (ng/mL)	−0.003	−0.006, −0.001	0.01
ApoA-I (mg/dL)	−0.004	−0.008, −0.001	0.03
hsCRP (mg/L)	−0.026	−0.050, −0.002	0.04

Based on mean values

ApoA-I apolipoprotein A-I, *CI* confidence interval, *hsCRP* high sensitivity C-reactive protein, *IL* interleukin, *MeanMax* mean of maximum, *PLA₂* phospholipase A₂, *SBP* systolic blood pressure, *SD* standard deviation, *TBR* target to background ratio

^a Adjusted for all other variables

Table 3

Baseline variables associated ($p < 0.05$) with change in carotid WA and TVA over 24 months by MRI, plus randomized treatment

	Coefficient	95 % CI	<i>p</i> value ^a
Association with change in carotid WA			
Dalcetrapib treatment	−2.624	−5.261, 0.013	0.05
Wall thickness (mm)	−17.928	−23.231, −12.625	<0.0001
PAI-1 activity (IU/mL)	0.251	0.101, 0.402	0.0014
Age (years)	0.204	0.043, 0.365	0.02
Association with change in TVA			
Dalcetrapib treatment	−4.414	−7.506, −1.323	0.0057
WA (mm ²)	−0.535	−0.734, −0.336	<0.0001
PAI-1 activity (IU/mL)	0.419	0.240, 0.598	<0.0001
Age (years)	0.264	0.751, 0.453	0.0068
Gender	−4.413	−8.364, −0.461	0.03

Based on mean values

CI confidence interval, TVA total vessel area, PAI-1 plasminogen activator inhibitor-1, WA wall area

^a Adjusted for all other variables in the set