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Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Fayad ZA, Mani V, Woodward M, et al, for the 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; published online Sept 12. DOI:10.1016/S0140-6736(11)61383-4.

Table e1. Changes in biomarkers of inflammation, oxidation and cardiovascular risk during the study period.

	Baseline absolute mean (SE)	Month 3		Month 12		Month 24	
		Mean (SE)	LSM (SE) % change from baseline	Mean (SE)	LSM (SE) % change from baseline	Mean (SE)	LSM (SE) % change from baseline
IL6, pg/mL[†]							
Placebo	3.86 (0.79)	2.87 (0.29)	20.73 (39.38)	3.34 (0.38)	56.73 (22.08)	2.59 (0.23)	6.32 (14.11)
Dalcetrapib	3.68 (0.36)	5.67 (1.12)	84.83 (40.10)	4.40 (0.65)	37.48 (21.46)	4.54 (0.70)	27.47 (13.81)
sP-Selectin, ng/mL[†]							
Placebo	71.87 (3.01)	76.20 (3.65)	6.08 (2.44)	79.09 (4.24)	7.28 (2.66)	76.93 (3.75)	7.27 (2.89)
Dalcetrapib	74.64 (2.66)	74.94 (2.83)	1.75 (2.48)	74.88 (3.03)	-0.36 (2.59)	73.63 (2.95)	1.26 (2.82)
sE-Selectin, ng/mL[†]							
Placebo	41.45 (2.07)	46.31 (2.73)	11.57 (2.12)	45.65 (3.49)	8.17 (2.63)	43.15 (3.05)	3.46 (3.47)
Dalcetrapib	41.06 (1.87)	44.13 (2.28)	6.84 (2.15)	43.90 (2.39)	7.93 (2.55)	43.39 (3.13)	5.08 (3.39)
Soluble Intracellular Adhesion Molecule, ng/mL[‡]							
Placebo	237.64 (9.11)	240.75 (9.42)	4.07 (1.85)	239.37 (9.75)	2.03 (1.85)	234.27 (9.81)	0.15 (2.29)
Dalcetrapib	239.38 (7.71)	238.54 (8.75)	0.97 (1.88)	236.25 (8.44)	0.69 (1.78)	236.67 (8.74)	-0.45 (2.23)
Soluble Vascular Cell Adhesion Molecule, ng/mL[‡]							
Placebo	857.14 (32.41)	863.22 (32.64)	4.45 (1.71)	852.29 (36.33)	4.30 (2.33)	860.42 (36.14)	4.95 (2.08)

Dalcetrapib	784.73 (22.12)	782.39 (22.52)	2.16 (1.73)	790.35 (20.96)	4.96 (2.23)	789.40 (23.80)	4.44 (2.02)
Phospholipase A2s, ng/mL[§]							
Placebo	189.39 (5.07)	184.24 (4.49)	-0.43 (2.23)	177.98 (5.26)	-1.66 (2.59)	182.87 (5.63)	-0.36 (2.49)
Dalcetrapib	199.30 (5.64)	207.47 (6.87)	7.26 (2.28)	215.00 (7.78)	10.86 (2.52)	211.50 (7.71)	9.03 (2.44)
Matrix-metalloproteinase-3, ng/mL[†]							
Placebo	20.07 (1.61)	19.19 (1.17)	4.77 (3.20)	18.59 (1.20)	4.38 (3.64)	20.23 (1.41)	19.80 (6.78)
Dalcetrapib	18.51 (1.08)	19.29 (1.11)	6.84 (3.25)	18.54 (1.13)	3.37 (3.53)	19.91 (1.22)	13.15 (6.61)
Matrix-metalloproteinase-9, ng/mL[†]							
Placebo	565.92 (40.54)	607.37 (46.75)	29.10 (7.44)	642.90 (52.19)	28.79 (11.83)	558.81 (35.80)	18.45 (9.94)
Dalcetrapib	544.67 (38.00)	521.41 (34.77)	11.30 (7.57)	564.53 (42.26)	25.06 (11.49)	568.85 (33.47)	33.27 (9.69)
Myeloperoxidase, pmol/L[‡]							
Placebo	1438.11 (786.00)	630.98 (55.13)	-1.94 (5.99)	1177.18 (493.1)	42.90 (26.76)	662.83 (66.98)	2.73 (8.49)
Dalcetrapib	675.05 (58.96)	597.61 (38.30)	0.75 (6.09)	567.60 (34.18)	4.43 (25.61)	553.87 (33.98)	1.76 (8.28)
Tissue plasminogen activator, ng/mL[#]							
Placebo	7.51 (1.51)	7.06 (1.12)	13.95 (8.45)	6.76 (0.91)	38.33 (12.49)	6.52 (0.80)	37.27 (10.99)
Dalcetrapib	6.56 (0.73)	6.92 (0.94)	7.29 (8.59)	7.31 (0.92)	22.29 (11.98)	6.75 (0.75)	4.57 (10.72)
Plasminogen activator inhibitor 1 – antigen, ng/mL[#]							
Placebo	60.16 (5.14)	60.73 (5.87)	9.82 (9.09)	68.52 (5.42)	26.79 (8.92)	57.30 (5.45)	9.40 (9.67)
Dalcetrapib	65.51 (5.86)	73.88 (6.66)	29.29 (9.22)	69.77 (5.53)	22.71 (8.53)	70.10 (6.17)	23.08 (9.42)

Plasminogen activator inhibitor 1 – activity, IU/mL[#]							
Placebo	15.14 (1.07)	16.38 (1.23)	11.35 (8.96)	17.79 (1.17)	19.04 (7.30)	15.31 (1.18)	5.19 (9.78)
Dalcetrapib	16.67 (1.09)	18.32 (1.21)	24.82 (9.03)	18.75 (1.14)	20.34 (6.94)	18.05 (1.23)	16.80 (9.47)

LSM, least squares mean; SE, standard error

[†]At baseline: placebo n=64, dalcetrapib n=63; for subsequent LSM comparisons: placebo n=59, dalcetrapib n=59 (3 months); placebo n=50, dalcetrapib n=55 (12 months); placebo n=48, dalcetrapib n=52 (24 months).

[‡]At baseline: placebo n=64, dalcetrapib n=63; for subsequent LSM comparisons: placebo n=59, dalcetrapib n=59 (3 months); placebo n=49, dalcetrapib n=55 (12 months); placebo n=48, dalcetrapib n=52 (24 months).

[§]At baseline: placebo n=64, dalcetrapib n=63; for subsequent LSM comparisons: placebo n=58, dalcetrapib n=59 (3 months); placebo n=49, dalcetrapib n=55 (12 months); placebo n=47, dalcetrapib n=52 (24 months).

[#]At baseline: placebo n=64, dalcetrapib n=63; for subsequent LSM comparisons: placebo n=59, dalcetrapib n=59 (3 months); placebo n=48, dalcetrapib n=54 (12 months); placebo n=48, dalcetrapib n=52 (24 months).

Table e2. Absolute (a) and percent (b) change from baseline in PET/CT measurements of inflammation after 3 and 6 months (index vessel)
(a)

Variable	LSM (SE) absolute change from baseline		Absolute change from baseline relative to placebo (90%CI)	p value[†]
	Placebo	Dalcetrapib		
Mean of maximum TBR				
Month 3	-0.07 (0.05)	-0.10 (0.05)	-0.03 (-0.15, 0.10)	0.73
Month 6	-0.15 (0.07)	-0.05 (0.07)	0.09 (-0.07, 0.26)	0.36
Mean of mean TBR				
Month 3	-0.01 (0.04)	-0.05 (0.04)	-0.04 (-0.12, 0.04)	0.43
Month 6	-0.04 (0.05)	-0.01 (0.05)	0.04 (-0.07, 0.14)	0.59

(b)

Variable	LSM (SE) percent change from baseline		Percent change from baseline relative to placebo (90%CI)	p value[†]
	Placebo	Dalcetrapib		
Mean of maximum TBR				
Month 3	-1.3	-2.0	-0.7 (-5.5, 4.0)	0.81
Month 6	-3.7	0.7	4.4 (-2.2, 11.0)	0.27
Mean of mean TBR				
Month 3	0.6	-0.6	-1.2 (-5.7, 3.2)	0.65
Month 6	-1.0	2.6	3.3 (-3.3, 9.9)	0.41

CI = confidence interval, LSM = least squares mean, SE = standard error, TBR = target to background ratio
[†]P-values (2-sided) are presented for the difference between arms

Table e3. Absolute (a) and percent (b) change from baseline in PET/CT measurements of inflammation after 3 and 6 months (average carotid)
(a)

Variable	LSM (SE) absolute change from baseline		Absolute change from baseline relative to placebo (90%CI)	p value[†]
	Placebo	Dalcetrapib		
Mean of maximum TBR				
Month 3	0.04 (0.05)	-0.01 (0.05)	-0.05 (-0.17, 0.07)	0.51
Month 6	0.04 (0.05)	-0.07 (0.05)	-0.12 (-0.23, 0.00)	0.12
Mean of mean TBR				
Month 3	0.03 (0.04)	-0.00 (0.04)	-0.04 (-0.12, 0.06)	0.52
Month 6	0.05 (0.04)	-0.06 (0.04)	-0.11 (-0.21, -0.01)	0.07

(b)

Variable	LSM (SE) percent change from baseline		Percent change from baseline relative to placebo (90%CI)	p value[†]
	Placebo	Dalcetrapib		
Mean of maximum TBR				
Month 3	3.2	-2.9	-2.5 (-8.4, 3.7)	0.50
Month 6	3.2	0.6	-5.9 (-11.5, 0.1)	0.10
Mean of mean TBR				
Month 3	3.1	0.6	-2.4 (-8.1, 3.7)	0.51
Month 6	4.2	-2.6	-6.5 (-11.9, -0.7)	0.07

CI = confidence interval, LSM = least squares mean, SE = standard error, TBR = target to background ratio
[†]P-values (2-sided) are presented for the difference between arms

Table e4. Per protocol population change from baseline in MRI measurements of plaque burden after 12 and 24 months (average carotid) and most diseased segment mean of maximum TBR at 6 months (index vessel)

	Baseline, mean (SE)	Absolute, mean (SE)	Absolute change* from baseline, mean (SE)	Absolute change† from baseline relative to placebo, mean (90% CI)	p
MRI					
Total vessel area at 12 months, mm^2					
Placebo (n=40)	61.96 (2.15)	63.04 (1.97)	1.39 (1.30)		
Dalcetrapib (n=44)	61.08 (2.04)	62.13 (2.17)	1.51 (1.28)	0.12 (-2.73, 2.96)	0.95
Total vessel area at 24 months, mm^2					
Placebo (n=39)	61.71 (2.26)	67.53 (2.34)	5.72 (1.45)		
Dalcetrapib (n=44)	59.56 (1.86)	61.44 (1.87)	1.71 (1.43)	-4.01 (-7.23, -0.80)	0.041
Wall area at 12 months, mm^2					
Placebo (n=40)	30.74 (1.52)	28.09 (1.02)	-1.86 (0.90)		
Dalcetrapib (n=44)	28.77 (1.10)	28.54 (1.08)	-0.10 (0.88)	1.77 (-0.21, 3.74)	0.14
Wall area at 24 months, mm^2					
Placebo (n=39)	30.33 (1.53)	32.28 (1.43)	2.69 (1.05)		
Dalcetrapib (n=44)	28.10 (1.01)	28.57 (0.86)	0.49 (1.04)	-2.20 (-4.54, 0.13)	0.12
Wall thickness at 12 months, mm					
Placebo (n=40)	1.27 (0.05)	1.14 (0.03)	-0.09 (0.03)		
Dalcetrapib (n=44)	1.18 (0.03)	1.16 (0.03)	-0.02 (0.03)	0.07 (0.01, 0.13)	0.046
Wall thickness at 24 months, mm					

Placebo (n=38)	1.26 (0.05)	1.27 (0.04)	0.05 (0.03)		
Dalcetrapib (n=44)	1.17 (0.03)	1.19 (0.03)	0.02(0.03)	-0.03 (-0.11, 0.04)	0.45
Normalised wall index at 12 months, %					
Placebo (n=40)	49 (1)	44 (1)	-3.2 (0.7)		
Dalcetrapib (n=44)	46 (1)	46 (1)	-0.8 (0.7)	2.4 (0.7, 4.0)	0.02
Normalised wall index at 24 months, %					
Placebo (n=39)	48 (1)	47 (1)	-0.4 (0.8)		
Dalcetrapib (n=44)	47 (1)	47 (1)	0.3 (0.8)	0.6 (-1.2, 2.5)	0.57
PET/CT					
Most diseased segment mean of maximum TBR at 6 months					
Placebo (n=52)	2.78 (0.10)	2.54 (0.08)	-0.27 (0.08)		
Dalcetrapib (n=51)	2.76 (0.10)	2.56(0.10)	-0.19 (0.08)	0.08 (-0.10, 0.26)	0.483

SE = standard error; CI = confidence interval. TBR, target-to-background ratio. [*]Change defined, for each treatment, as follow-up value minus baseline value; [†]change relative to placebo defined as change for dalcetrapib minus change for placebo; corrected for baseline and centre.

Statistical Analysis Plan

Although the primary purpose of the study was to rule out a potential pathological vascular effect of dalcetrapib (following the results observed with torcetrapib), due to the sparseness of the literature reporting similar studies in 2006, when dal-PLAQUE was designed, little information was available on which to base no-harm boundaries. Traditional superiority testing was considered a suitable alternate approach, with the sample size nominally defined using informal power calculations as described by Fayad and colleagues.[1] Statistical methods for the analysis of primary and secondary endpoints in dal-PLAQUE also have been described therein. For analyses of primary and secondary endpoints, analysis of covariance, adjusting for baseline values and centre, was used to compare changes from baseline to follow-up between the intervention and control arms of the trial. Nominal p-values are presented throughout.

In the intervening years, more imaging data became available,[2–5] from which the observed rates of disease progression for the 18F-FDG-PET/CT and MRI parameters were used to guide the selection of no-harm boundaries to facilitate interpretation of the dal-PLAQUE co-primary endpoints. These “no-harm” boundaries were prospectively defined by the Executive Committee on November 13, 2010, prior to database lock and un-blinding. Based on the then available literature, it was decided by the committee to extend the time point for the primary MRI assessment of no harm from 12 months to 24 months of treatment in order to capture possible long-term effects. Individual limits of "no-harm" were calculated for each individual parameter as noted below.

PET/CT No Harm parameter:

The PET-CT no-harm parameter was derived from two prior observations. Firstly, Rudd et al reported that the 95% confidence interval (CI) for inter-scan variability for TBR measurements within the ascending aorta was approximately 10% of the baseline TBR value.6 Secondly, a recent study observed an approximately 10% decrease in arterial TBR (assessed by 18F-FDG-PET) after 6 months of treatment with atorvastatin 20 mg.[5] Based on these observations, we defined a 10% increase in the MDS TBR as the threshold to define a potentially important increase in TBR. Applied to the average baseline value for MDS TBR from dal-PLAQUE (2.7), a 10% change corresponds to an absolute change of 0.27. Therefore, for the co-primary 18F-FDG-PET endpoint, “no harm” was to be concluded if the upper limit of the CI for the absolute change from baseline relative to placebo in the mean of the maximum MDS TBR does not exceed 0.27 after 6 months of dalcetrapib treatment.

MRI No-Harm parameters:

For the pre-specified co-primary MRI endpoint of change from baseline in atherosclerotic plaque burden as measured by four indices, the following describes the choice of no-harm boundaries.

Total Vessel Area: In a retrospective analysis of patients at risk for atherosclerosis receiving current standard of care who underwent serial MRI assessments, an absolute average increase by +1.0 mm^2 over one year was observed.[2] Thus, progression by more than +2.0 mm^2 over a period of 24 months was considered of possible clinical relevance and used as no-harm threshold.

Wall Area: In the Oxford Niaspan Study,4 a mean progression per year of +1.64 mm^2 was observed. Consistent with that, the paper by Hayashi et al[2] reported annual progression of +1.53 mm^2. Assuming linearity over time, being able to statistically rule out progression by more than 3 mm^2 over a period of 24 months was thus considered to allow the conclusion of no harm.

Wall Thickness: In the ORION trial3 an absolute increase of +0.02 mm over 2 years was observed in patients with moderate hypercholesterolaemia and documented carotid stenosis treated with rosuvastatin (average from the combined 5 mg and 40/80 mg arms).

Normalised Wall Index: Hayashi et al 20102 reported progression of +0.02 (2%) per year. Extrapolation to a 2-year period thus leads to an expected progression of +0.04 (4%) and thus ensuring that the effect of dalcetrapib does not exceed that value was considered clinically relevant.

As the observed baseline means and standard deviations in these studies corresponded in magnitude to those in dal-PLAQUE, “no harm” was to be concluded if the upper limit of the CI for the absolute change from baseline (relative to placebo) does not exceed 2.0 mm^2 for total vessel area, 3.0 mm^2 for wall area, 0.02 mm for wall thickness, and 0.04 (4%) for normalised wall index after 2 years of dalcetrapib treatment.

No formal criteria for assessment of the abdominal aorta were established due to the sparseness of data in this area. Although the analysis plan called for one-sided tests of the effects of dalcetrapib, here we present two-sided tests of efficacy for consistency throughout the text and to align with standard presentations. However, so as to enable 5% one-sided tests to be evaluated, 90% two-sided CI are included. Primary analyses were carried out as intent-to-treat (ITT) using the observed cases method (ie, only patients who had data at the time point being assessed were included in the analysis) and included all randomised patients.

An analysis of the relationship between the change in HDL and the change in the co-primary imaging parameters was pre-specified. Additionally, a limited number of post hoc analyses were performed for this initial study report. Specifically, we evaluated: 1) the relationship between the carotid MDS TBR and HDL-C concentration, and 2) relationships between the MR and PET imaging variables that showed significant or near-significant treatment effects in the efficacy analysis.

References

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3. Underhill HR, Yuan C, Zhao XQ et al. Effect of rosuvastatin therapy on carotid plaque morphology and composition in moderately hypercholesterolemic patients: a high-resolution magnetic resonance imaging trial. Am Heart J. 2008;155:584.e1-8. Erratum in: Am Heart J. 2008;**155**:1127

4. Lee JM, Robson MD, Yu LM et al. Effects of high-dose modified-release nicotinic acid on atherosclerosis and vascular function: a randomized, placebo-controlled, magnetic resonance imaging study. *J Am Coll Cardiol* 2009;**54**:1787-1794

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6. Rudd JH, Myers KS, Bansilal S et al. (18)Fluorodeoxyglucose positron emission tomography imaging of atherosclerotic plaque inflammation is highly reproducible: implications for atherosclerosis therapy trials. *J Am Coll Cardiol* 2007;**50**:892-896

Figure 1e. Top Row: Baseline non-contrast enhanced CT images of a patient with extensive atherosclerosis in the dal-PLAQUE study. Axial (left), coronal (centre) and higher magnification axial images (right) demonstrating bilateral carotid artery calcification more marked in the right carotid artery. **Bottom Row: Baseline fused FDG-PET and CT from the same patient shown in the top row.** Axial (left), coronal (centre) and higher magnification axial images (right) demonstrating bilateral carotid artery calcification more marked in the right carotid artery. In addition, the red/orange regions represent FDG uptake (yellow arrows). This appears more marked in the right than the left carotid (coronal view). The bottom right panel also shows a typical placement of regions of interest (ROI) on the vessel to allow measurement of FDG uptake within the carotid artery (C: target) and jugular vein (V: background). The standardised uptake value (SUV) was the decay-corrected tissue concentration of FDG (in kBq/ml) divided by the injected dose per body weight (kBq/g). The formulae for calculating target to background ratio (TBR) is as follows: TBR = SUV-target/ SUV-background.

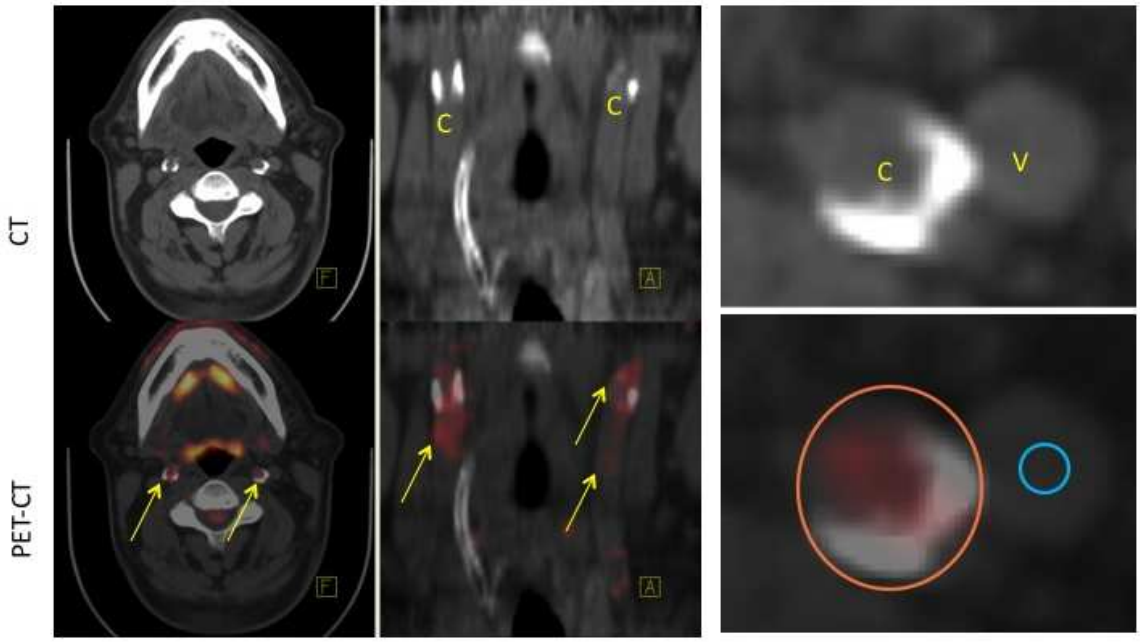


Figure 2e. Stylised diagram of an artery to demonstrate the various PET indices that are derived from the regions of interest (ROI) placed on the vessel. A circular ROI is drawn to encompass the vessel wall on each contiguous axial segment. Each axial segment then provides two numbers: a mean and a maximal value for the FDG uptake within that segment, expressed as the TBR. The MeanMean TBR is the averaged Mean TBR values from each artery. The MeanMax TBR is the averaged Max TBR values from each artery. The most diseased segment (MDS) is centred on the darkest red segment, defined as having the highest maximal TBR value in the entire artery. When averaged with the segments immediately above and below it, these three segments yield the MDS. Example values and their derivations are provided in the lowest row

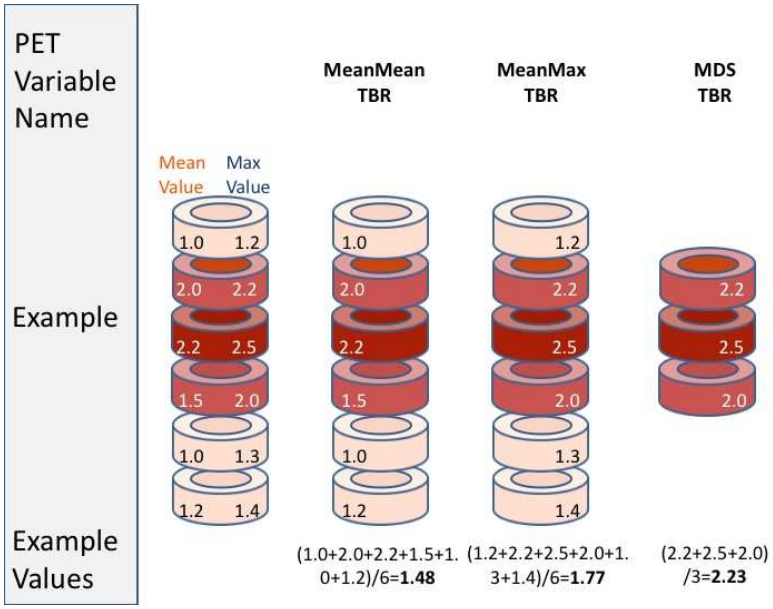


Figure 3e. Sample MRI images from a patient at baseline (left) and treated with dalcetrapib 600 mg for 24 months (right) showing regression in total vessel area (top panel). The MRI metrics used as endpoints are shown in the bottom panel. LCC = left carotid artery. RCC = right carotid artery. Wall outer boundary is denoted in green. Wall inner boundary is denoted in yellow. Total vessel area is lumen area + wall area. Normalised wall index is wall area divided by total vessel area and represents a ratio with no units.

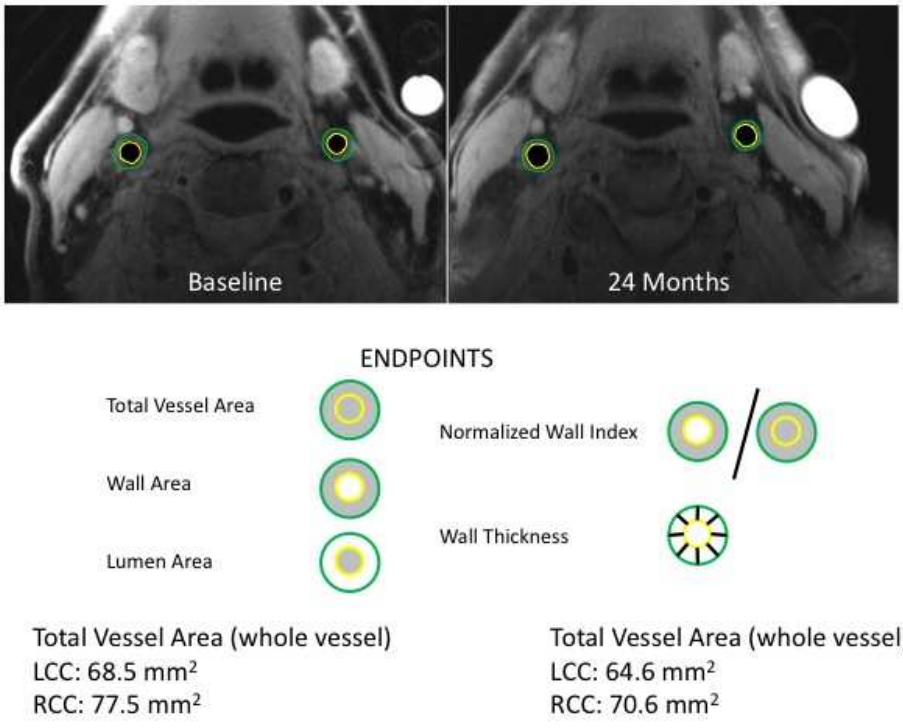
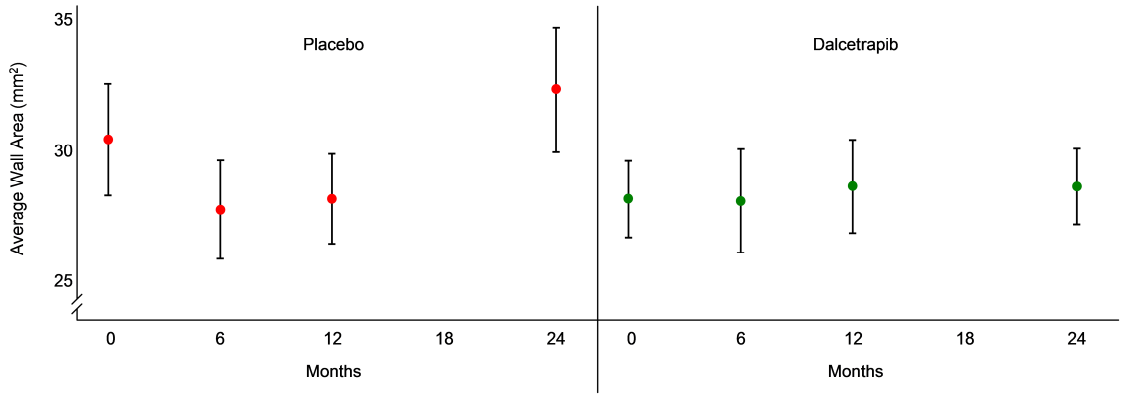


Figure 4e (a) Mean and (b) percent change in wall area (by MRI)

a)



b)

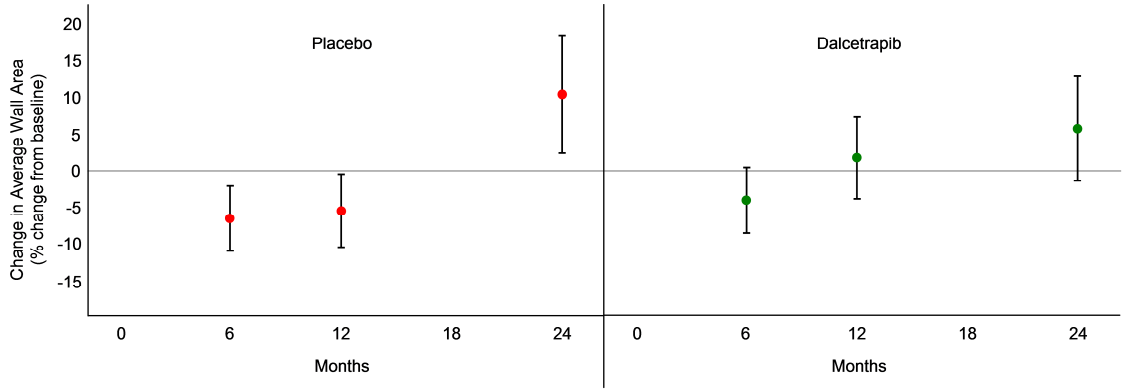
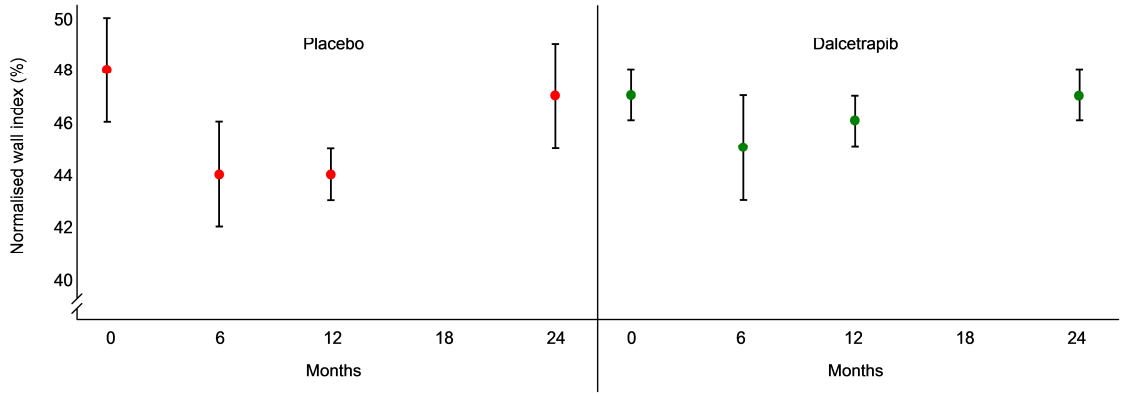


Figure 4e (a) shows the raw mean data (90% CI) for average wall area at baseline, 6, 12 and 24 months. In comparison with placebo, there was a numerical reduction in wall area with dalcetrapib after 24 months, with an absolute change (90% CI) from baseline relative to placebo of -2.20 mm^2 (-4.53, 0.13), p=0.12.

Figure 4e (b) shows the mean (90%CI) percent change in wall area at 6, 12 and 24 months (relative to baseline). For patients in the dalcetrapib group, the estimated percent change from baseline relative to placebo (90% CI) after 24 months was -6.9% (-16.0, 2.3), p=0.22.

Figure 5e (a) Mean and (b) percent change in normalised wall index (by MRI)

a)



b)

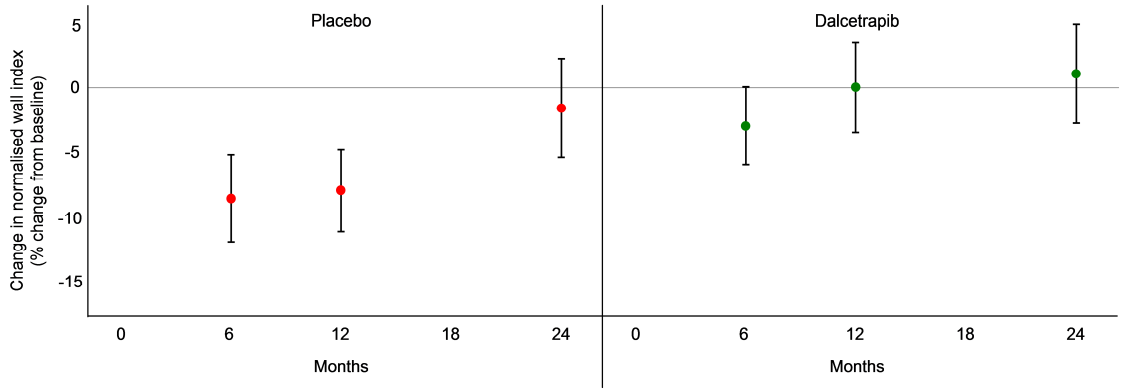
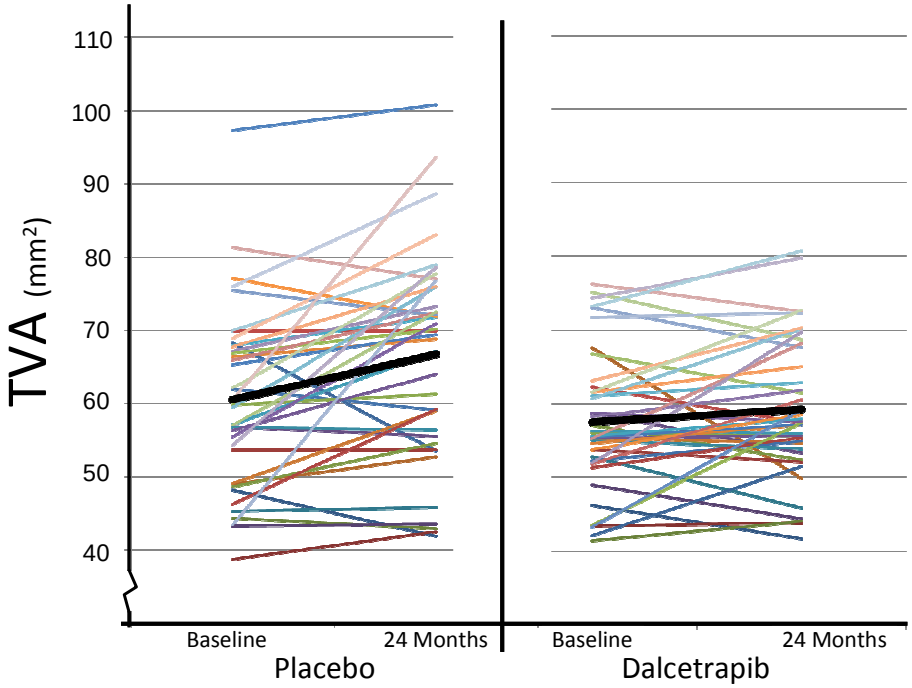


Figure 5e (a) shows the mean data (90% CI) for the normalised wall index at baseline, 6, 12 and 24 months. The dalcetrapib change from baseline, relative to placebo, was 0.6% (-1.2, 2.5) after 24 months, p=0.57.

Figure 5e (b) illustrates the mean (90% CI) percent change from baseline at 6, 12 and 24 months. For patients in the dalcetrapib group, the estimated percent change from baseline relative to placebo (90% CI) after 24 months was 1.6% (-2.5, 6.0), p=0.52.

Figure 6e. Individual patient data for a) absolute change in average carotid total vessel area (by MRI) and b) absolute change in average carotid most diseased segment TBR (by PET).

a)



b)

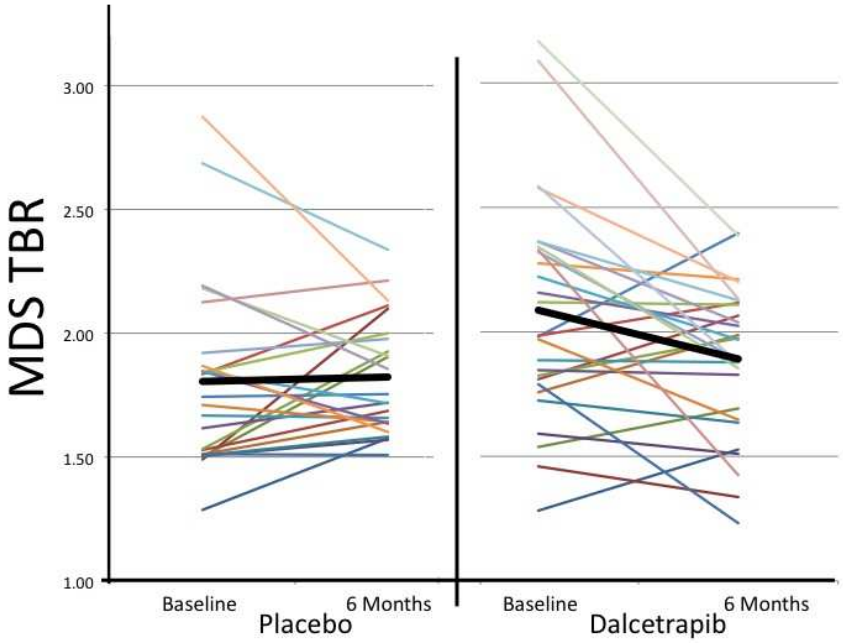


Figure 6e(a) Shows the individual patient data for total vessel area (TVA) at baseline and 24 months. The TVA, an index of atherosclerotic burden, increased after 24 months in the placebo group: average absolute change (90% CI) for TVA, (24 months - baseline), 5.72 (3.30, 8.14), p=0.0002. However, in the dalcetrapib group, TVA did not change over the same period: 1.71 (-0.68, 4.10), p=0.24. The average (90%CI) reduction in TVA on dalcetrapib (versus placebo), after correction for baseline, was -4.01 (-7.23, -0.80), p=0.04. Figure 6e(b) shows the individual patient data average carotid most diseased segment (MDS) TBR at baseline and 6 months. In the placebo group, MDS TBR did not change after 6 months: average absolute change (90%CI) for MDS TBR (6 months - baseline), -0.043 (-0.14, 0.06), p=0.48. However, in the dalcetrapib group, MDS TBR decreased over the same period: -0.19 (-0.29, -0.09), p=0.001. The average (90%CI) reduction in MDS TBR on dalcetrapib (versus placebo), after correction for baseline, was -0.150 (0-0.29, -0.01), p=0.08.

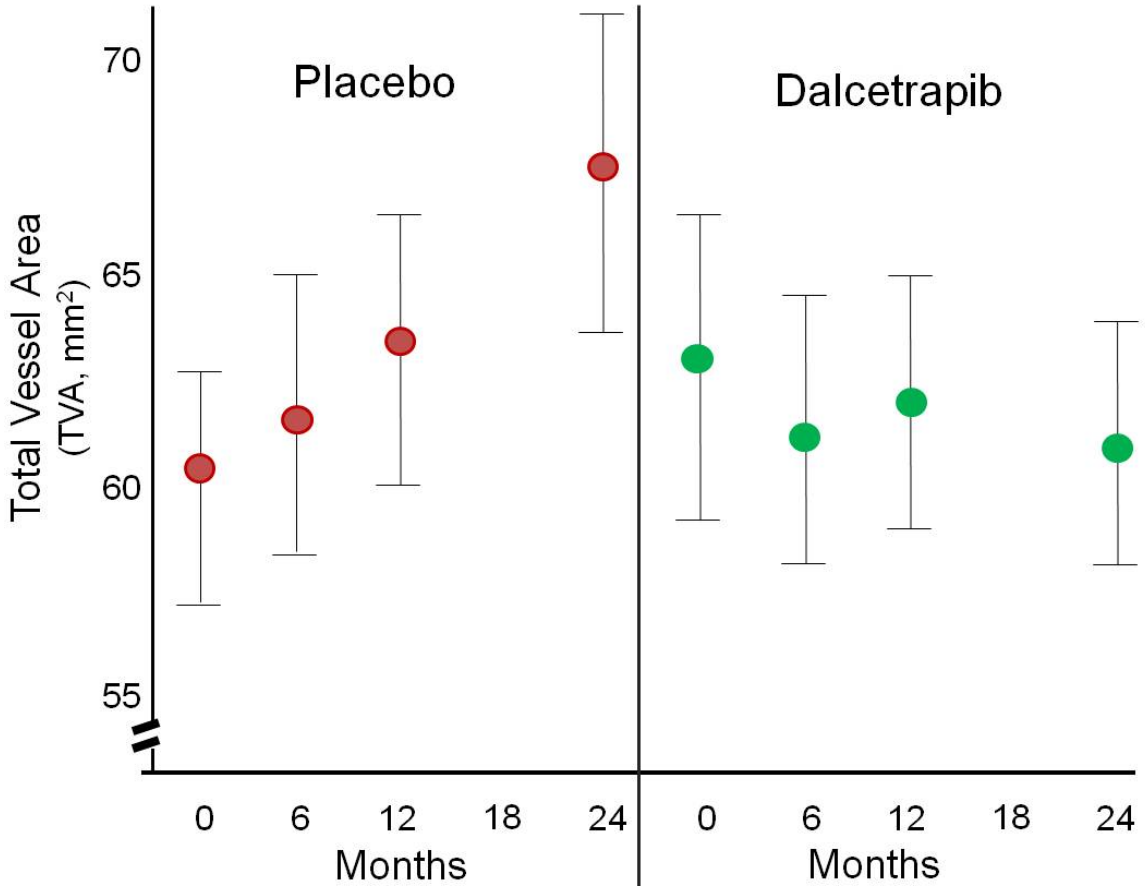


Figure 7e (a) Shows the raw mean data limited to subjects that provided imaging data for all MRI imaging time points , thus providing further assessment of temporal changes in TVA.

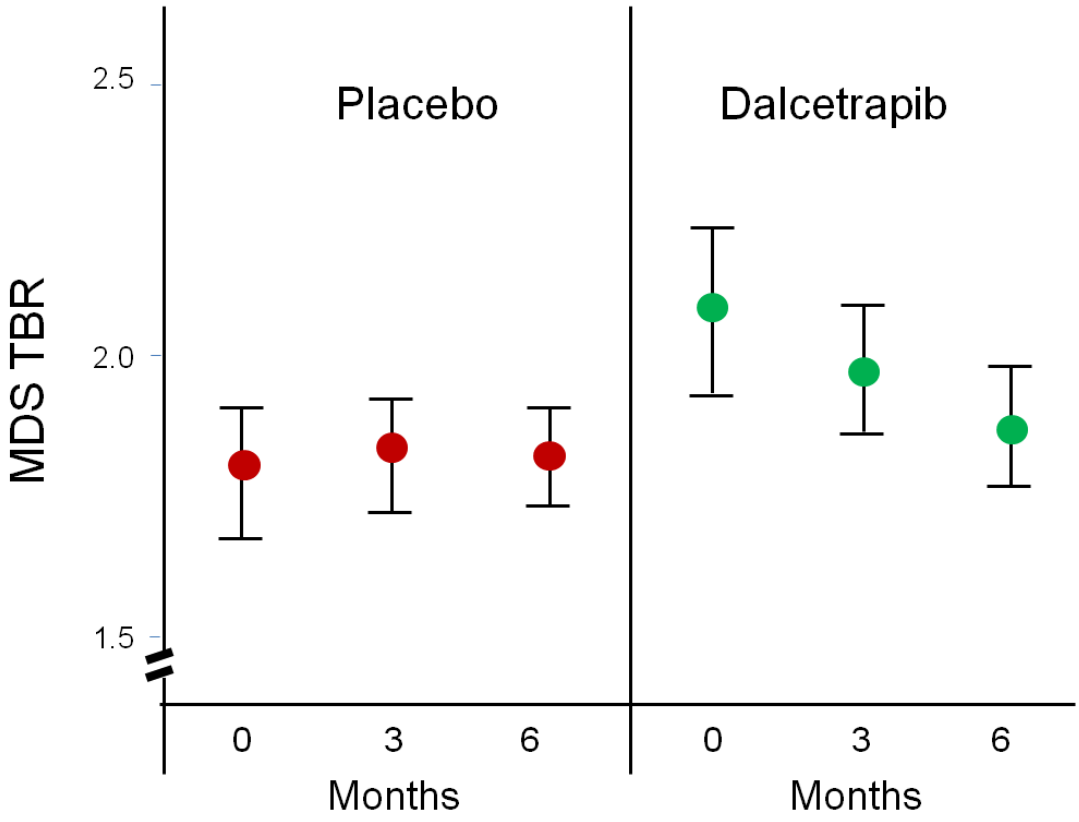


Figure 7e (b) Shows the raw mean data limited to subjects that provided imaging data for all PET imaging time points , thus providing further assessment of temporal changes in carotid MDS TBR.