Torcetrapib and carotid intima-media thickness in mixed dyslipidaemia (RADIANCE 2 study): a randomised, double-blind trial

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Summary

Background Patients with mixed dyslipidaemia have raised triglycerides, low high-density lipoprotein (HDL) cholesterol, and high low-density lipoprotein (LDL) cholesterol. Augmentation of HDL cholesterol by inhibition of the cholesteryl ester transfer protein (CETP) could benefit these patients. We aimed to investigate the effect of the CETP inhibitor, torcetrapib, on carotid atherosclerosis progression in patients with mixed dyslipidaemia.

Methods We did a randomised double-blind trial at 64 centres in North America and Europe. 752 eligible participants completed an atorvastatin-only run-in period for dose titration, after which they all continued to receive atorvastatin at the titrated dose. 377 of these patients were randomly assigned to receive 60 mg of torcetrapib per day and 375 to placebo. We made carotid ultrasound images at baseline and at 6-month intervals for 24 months. The primary endpoint was the yearly rate of change in the maximum intima-media thickness of 12 carotid segments. Analysis was restricted to 683 patients who had at least one dose of treatment and had at least one follow-up carotid intima-media measurement; they were analysed as randomised. Mean follow-up for these patients was 22 (SD 4·8) months. This trial is registered with ClinicalTrials.gov, number NCT00134238.

Findings The change in maximum carotid intima-media thickness was 0·025 (SD 0·005) mm per year in patients given torcetrapib with atorvastatin and 0·030 (0·005) mm per year in those given atorvastatin alone (difference −0·005 mm per year, 95% CI −0·018 to 0·008, p=0·46). Patients in the combined-treatment group had a 63·4% relative increase in HDL cholesterol (p<0·0001) and an 17·7% relative decrease in LDL cholesterol (p<0·0001), compared with controls. Systolic blood pressure increased by 6·6 mm Hg in the combined-treatment group and 1·5 mm Hg in the atorvastatin-only group (difference 5·4 mm Hg, 95% CI 4·3–6·4, p<0·0001).

Interpretation Although torcetrapib substantially raised HDL cholesterol and lowered LDL cholesterol, it also increased systolic blood pressure, and did not affect the yearly rate of change in the maximum intima-media thickness of 12 carotid segments. Torcetrapib showed no clinical benefit in this or other studies, and will not be developed further.

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Introduction

Mixed dyslipidaemia is often seen as part of a cluster of vascular risk factors, closely related to insulin resistance and abdominal obesity, known as metabolic syndrome.[1] Patients with metabolic syndrome are at increased risk of future cardiovascular events.[2–4] The pandemic of obesity has caused a noticeable increase in the rate of the metabolic syndrome and type 2 diabetes.[2] These disorders are typically associated with an atherogenic dyslipidaemia characterised by hypertriglyceridaemia, reduced high density lipoprotein (HDL) cholesterol, a preponderance of small, dense low-density lipoprotein (LDL) cholesterol particles and high concentrations of cholesterol-rich remnant particles.[2,5,6] Atherogenic dyslipidaemia is linked with an increased risk of atherosclerotic vascular disease.[3,4] Lifestyle modification and lowering of blood pressure and LDL cholesterol can reduce risk.[7] Treatments to increase low HDL cholesterol could further reduce risk.[8]

Several lines of evidence suggest that HDL cholesterol has a role in cardiovascular risk. A low HDL cholesterol concentration is an established vascular risk factor.[3,4,9] Drugs such as nicotinic acid and fibrates increase HDL cholesterol by 10–25%[8] and augmentation of HDL cholesterol could contribute to reduction of vascular risk[10–12] and attenuate progression of atherosclerosis.[12–14]

The cholesteryl ester transfer protein (CETP) regulates plasma HDL cholesterol concentration. CETP can transfer cholesterol esters from HDL particles to lipoproteins that contain apolipoprotein B (apoB), such as very low density lipoprotein and LDL, in exchange for triglycerides.[8,15] People who have a genetically low expression of CETP have high concentrations of HDL cholesterol.[16] Conversely, patients with mixed dyslipidaemia have high CETP concentrations and activity, and low HDL cholesterol.[17,18] The net transfer of cholesterol esters from HDL cholesterol to lipoproteins containing apo B is much higher in patients with mixed dyslipidaemia than in normolipidaemic individuals.[19] Since an increased transfer of cholesteryl esters out of HDL particles will cause low HDL cholesterol, inhibition of CETP could potentially raise HDL cholesterol concentrations and thereby protect against atherosclerosis.[7,20,21] Indeed, studies with CETP inhibitors have

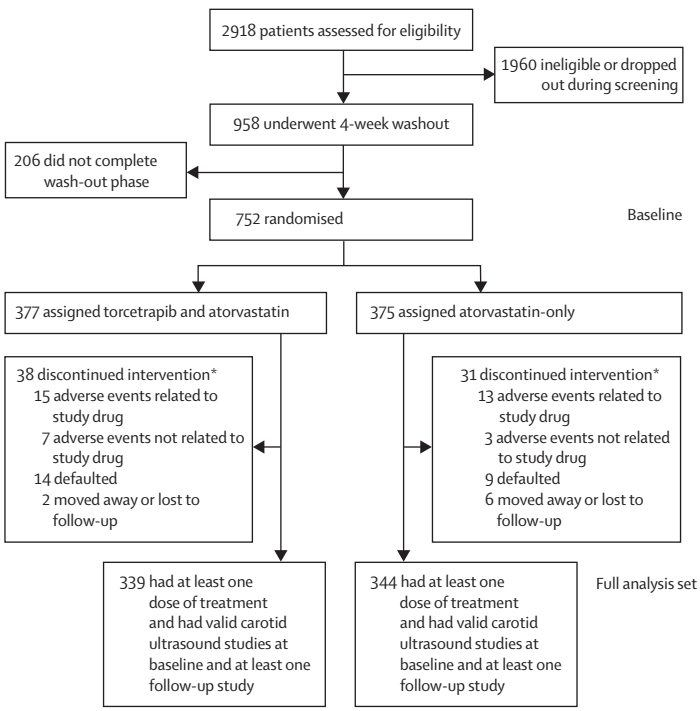

Figure 1: **Trial profile**
CIMT=carotid intima-media thickness. *These patients were excluded from the full analysis set because they did not have a baseline scan or at least one follow-up scan.

shown that they raised HDL cholesterol by 60% or more.[22,23] In studies of cholesterol-fed rabbits, CETP inhibition was profoundly antiatherogenic,[24] but this effect has not been shown in people.

We aimed to assess the effect of torcetrapib, a CETP inhibitor, on the progression of atherosclerosis in patients with mixed dyslipidaemia, by measuring the thickening of carotid intima-media, a marker of atherosclerosis. This study should, however, be viewed in the context of a randomised controlled trial[25] of the clinical effect of combined treatment with torcetrapib and atorvastatin on morbidity and mortality. That study was prematurely terminated because of an excess of all-cause mortality in patients given torcetrapib.[26]

Methods

Participants

64 recruitment and imaging centres in North America and Europe participated in a randomised, multicentre, parallel group trial, from Dec 1, 2003, to Dec 27, 2006.[27] Institutional review boards of all participating centres approved the protocol. 2918 patients aged 18–70 years were screened (figure 1). Eligibility criteria were triglycerides of greater than 1·7 mmol/L and a concurrent LDL cholesterol concentration that was high enough to qualify for statin treatment according to the guidelines of the US National Cholesterol Education Programme (NCEP) Adult Treatment Panel.[28]

958 eligible patients underwent a 4-week washout phase in which lipid-lowering treatment was discontinued, and had counselling about lifestyle changes for reduction of cardiovascular risk factors. These patients began an atorvastatin-only run-in period during which the atorvastatin dose was titrated to a target LDL cholesterol concentration according to individual cardiovascular risk on the basis of the NCEP guidelines. Therefore the dose of atorvastatin given during the trial was similar to the dose needed for each patient to achieve their target of LDL cholesterol less than 2·59, 3·37, or 4·14 mmol/L, dependent on their calculated cardiac risk during the run-in period.[27,28]

The 752 participants who successfully completed the run-in phase continued to be given atorvastatin once daily at the dose established during the run-in period. In addition to atorvastatin, 377 patients were randomly assigned to receive 60 mg torcetrapib every day, and 375 to receive corresponding placebo tablets once daily. The placebo tablets were identical in appearance to active torcetrapib tablets.

Patients were randomised by use of a central scheme with a computer-generated permuted block design, and a block size of four. Blocks were stratified by geographic region (North America or Europe) and atorvastatin dose at the end of the run-in period (10, 20, 40, or 80 mg). Sample sizes within strata were not restricted. Participants and study personnel were unaware of treatment assignment, laboratory measurements, and carotid imaging findings.

Procedures

Our ultrasound protocol for assessment of carotid intima-media thickness has been described in detail elsewhere.[27,29] In short, we made replicate scans at baseline and at each patient's final visit, and made single scans at visits at 6, 12, and 18 months, to give a maximum of seven scans for each patient. At each visit we acquired circumferential images of the right and left common carotid artery, bifurcation, and the near and far walls of the internal carotid artery. All imaging centres used the same imaging acquisition protocol and equipment (Sequoia 512 scanners equipped with 8L5 transducers; Siemens AG, Munich, Germany). 48 5-s image sequences were saved in DICOM format (Digital Imaging in Communications in Medicine, National Electrical Manufacturers Association, Rosslyn, VA, USA).

Imaging data were transferred directly from the study sites to the two reading centres (Vascular Imaging Center, University Medical Center, Utrecht, Netherlands, and Wake Forest University Medical Center, Ultrasound Reading Center, Winston-Salem, NC, USA), where standardised equipment and protocols were used to process stored images. From every image sequence, readers selected one frame in end diastole for measurement of carotid intima-media thickness. Maximum thickness (and also mean for the common carotid artery) was measured semiautomatically with

Artery Measurement System software (Chalmers University, Göthenburg, Sweden).[30] Readers were unaware of the interventions assigned to patients, and of previous measurements.

Quality assurance protocols have been described elsewhere.[27] Intraclass correlation coefficients, indicating the reproducibility of the mean maximum measurements between replicate scans at baseline (n=752) and final visit (n=634) were 0·92 and 0·91, respectively. (Not all the 683 patients who had valid carotid ultrasound studies at baseline and at least one follow-up visit had replicate scans at their final visit.) The intraclass correlation coefficient for monthly quality assurance scans (n=128) was 0·96.

The primary endpoint was the yearly change in the maximum intima-media thickness for the 12 carotid artery segments (near and far walls of the right and left common carotid artery, carotid bulb, and the internal carotid artery). Secondary endpoints included the yearly change in the maximum thickness, separately for the three carotid artery segments (common carotid artery, carotid bulb, and the internal carotid artery) and for the mean common thickness. Fasting blood samples were obtained for analysis of total cholesterol, HDL and LDL cholesterol, and triglycerides. At every visit, physicians assessed patients for adverse effects and did physical examinations, vital-sign measurements, urinalysis, and haematology.

Statistical methods

We calculated that a sample size of 336 patients in each treatment group was needed to provide 90% power to detect a difference of 0·015 mm in the yearly rate between the two treatment groups, assuming a common standard deviation of 0·06 mm per year and two-sided α of 0·05. We planned to recruit 840 participants to allow for withdrawal of about 20% during the 2-year course of treatment.

A linear mixed-effects model was used to analyse the yearly rate of change in maximum carotid intima-media thickness. The model consisted of 84 maximum measurements (seven scans of 12 segments) for every participant as the dependent variables, with random intercepts and slopes as a function of time and fixed effects for geographic region, atorvastatin dose at run-in, carotid segment, treatment, time, and time by treatment interaction. Testing was two-sided, with a 5% type I error rate.[31–33] Similar models were used to analyse secondary endpoints, except that only 28 maximum or mean measurements were used for each carotid segment (near and far wall on right and left sides over seven scans). We did prespecified exploratory analyses to see whether treatment effects for the primary endpoint differed across subgroups by use of multiplicative interaction terms.

Prespecified subgroups were age (≥65 years or <65 years); sex; race (white or non-white); HDL cholesterol (≥1·04 mmol/L or <1·04 mmol/L); LDL cholesterol (median and greater, or less than the median); metabolic syndrome (according to NCEP ATP III criteria); cigarette smoking; diabetes mellitus; history of hypertension; C-reactive protein (≥3·0 mg/L or <3·0 mg/L); and baseline maximum carotid intima-media thickness (median and greater, or less than the median). We have only reported subgroups for which a significant interaction was found.

	Atorvastatin monotherapy	Atorvastatin plus torcetrapib
All randomised patients (n=752)		
Age (years)	56·5 (8·2)	57·9 (8·1)
Sex (male)	245 (65%)	237 (63%)
Body-mass index (kg/height²)	30·0 (4·4)	30·0 (4·3)
History of diabetes	92 (25%)	68 (18%)
History of hypertension	185 (49%)	193 (51%)
Current smokers	58 (15%)	63 (17%)
Aspirin use at baseline	204 (54%)	209 (55%)
β blocker use at baseline	90 (24%)	111 (29%)
ACE or ARB use at baseline	138 (37%)	146 (39%)

Data are mean (SD) or number (%). ACE=angiotensin-converting enzyme inhibitor. ARB=angiotensin receptor blocker.

Table 1: **Baseline characteristics**

Role of the funding source

The study sponsor, Pfizer, collaborated with academic investigators in design of the study, and monitored the study. The study data were analysed independently by the sponsor, the core laboratories, and the principal investigators. The sponsor reviewed the manuscript and provided editorial comments to the lead authors. The corresponding author had full access to all the data in the study. The corresponding author made the final decision to submit for publication in collaboration with coauthors.

Results

Figure 1 shows the trial profile and table 1 shows demographic characteristics and medication at baseline. All torcetrapib–atorvastatin clinical trials were stopped on Dec 2, 2006, when an independent data safety and monitoring board for another study of torcetrapib and atorvastatin recommended that it be terminated because of an increase in deaths in the treatment group.[26] 48 participants who were still receiving treatment on that date were asked to discontinue treatment immediately and to return for final visits in that month as originally planned.

The titrated dose of atorvastatin averaged 13·3 (SD 10·6) mg in the combined-treatment group, and 13·2 (10·6) mg in the group given atorvastatin alone. Average doses of atorvastatin remained stable over the treatment period in both groups. After a mean follow-up of 20 (7·2) months, 314 patients in the combined-treatment group and 315 controls had a daily dose of 10 mg atorvastatin; 40 patients in each group had 20 mg; 17 and 14 patients, respectively, had 40 mg; and six in each group had 80 mg. Compliance with study drugs was greater than 80% in 710/736 (97%) patients.

	Atorvastatin monotherapy	Atorvastatin plus torcetrapib	p
Baseline (mm)			
Maximum over 12 segments	1·30 (0·29)	1·32 (0·32)	0·53
Maximum common carotid artery	1·15 (0·21)	1·15 (0·22)	0·79
Mean common carotid artery	0·83 (0·14)	0·83 (0·15)	0·98
24 month follow-up* (mm)			
Maximum over 12 segments	1·36 (0·31)	1·36 (0·31)	0·97
Maximum common carotid artery	1·18 (0·22)	1·19 (0·20)	0·54
Mean common carotid artery	0·84 (0·15)	0·85 (0·15)	0·40
Yearly change* (mm per year)			
Maximum over 12 segments	0·030 (0·005)	0·025 (0·005)	0·46
Mean common carotid artery	0·008 (0·002)	0·013 (0·002)	0·06
Maximum common carotid artery	0·020 (0·004)	0·022 (0·004)	0·65
Maximum carotid bifurcation	0·033 (0·008)	0·028 (0·008)	0·68
Maximum internal carotid artery	0·034 (0·007)	0·025 (0·007)	0·30

Data are mean (SD) or gradient (SE), unless otherwise specified. *A last observation carried forward (LOCF) technique was used for 24-month follow-up variables, but not for yearly change in carotid intima-media thickness.

Table 2: **Baseline, follow-up, and change from baseline in carotid intima-media thickness**

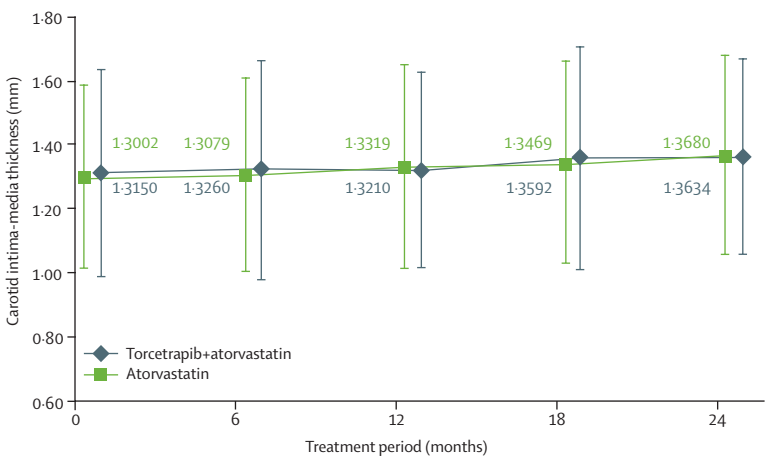

Figure 2: **Mean maximum carotid intima-media thickness during 24 months of treatment**
Bars represent SD.

The full analysis set incorporated all patients with at least one measurement of carotid intima-media thickness after baseline: 339 (90%) in the torcetrapib and atorvastatin group and 344 (92%) patients in the atorvastatin group. Table 2 and figure 2 show that the primary efficacy measure, the yearly rate of change in maximum carotid intima-media thickness, increased by 0·025 (SE 0·005) mm per year in patients given torcetrapib and atorvastatin and by 0·030 (0·005) mm per year in those given only atorvastatin. The difference between groups (–0·005 mm per year) was non-significant (95% CI –0·018 to 0·008, p=0·46).

The yearly rate of change in maximum carotid intima-media thickness differed for the prespecified subgroups of men or women (p=0·016); patients with or without metabolic syndrome (p=0·045); and those with a carotid intima-media thickness of greater than or less than the median (p=0·016). The difference in thickening of carotid intima-media between women given torcetrapib and atorvastatin and those given atorvastatin alone was –0·016 mm per year (95% CI –0·037 to 0·005); for men this difference was 0·001 mm per year (–0·016 to 0·017). In participants without metabolic syndrome, the difference in thickening of carotid intima-media between treatment groups was –0·010 mm per year (–0·027 to 0·006), compared with 0·002 mm per year (–0·019 to 0·023) in those with metabolic syndrome. In participants with a carotid intima-media thickness of less than the median at baseline, the difference between treatment groups was 0·011 mm per year (–0·003 to 0·025), compared with –0·020 mm per year (–0·042 to 0·002) in those whose baseline thickness was greater than the median.

Table 3 shows that concentrations of HDL cholesterol in patients given torcetrapib and atorvastatin increased from baseline during the study (p<0·0001), and that LDL cholesterol decreased in these patients (p<0·0001). In controls, HDL cholesterol did not change (p=0·1941) and LDL cholesterol changed by a small amount (p=0·0043) Patients assigned to receive torcetrapib and atorvastatin had a 63·4% relative increase in HDL cholesterol (95% CI 59·56–67·31, p<0·0001) and a 17·7% relative decrease in LDL cholesterol, compared with controls (–21·91 to –13·43, p<0·0001). Patients given combined treatment had a greater reduction in plasma triglycerides than did controls (p=0·0005).

Table 3 shows that during the trial, systolic blood pressure increased in both treatment groups, but more in the combined-treatment group, with an average difference between groups of 5·4 mm Hg (95% CI 4·3–6·4, p<0·0001). In the torcetrapib and atorvastatin group, the proportions of patients with systolic blood pressure of more than 140, 160, and 180 mm Hg at any visit were 8–14%, 0–1%, and 0%, respectively. In the group given atorvastatin alone the proportions with blood pressure of more than 140, 160, and 180 mm Hg were 3–5%, 0–1%, and 0–1%, respectively. No patients in either group had systolic blood pressure of more than 200 mm Hg. The frequency at which systolic blood pressure was raised by 15 mm Hg or more was 20/377 (5%) in the combined-treatment group and 8/375 (2%) in controls (p=0·02).

At baseline, concurrent use of antihypertensive agents was noted in 97/377 (26%) patients in the combined-treatment group and 115/375 (31%) controls. Since torcetrapib was associated with raised blood pressure, more patients assigned to combined treatment had been prescribed new antihypertensive drugs by final visit than had controls; 88/377 (23%) patients in the treatment group were on new antihypertensive drugs, compared with 47/375 (13%) controls.

Two patients died during the study: one in the torcetrapib and atorvastatin group, due to pneumonia, and one in the atorvastatin only group, due to a traffic

accident. 17 patients assigned to receive torcetrapib and atorvastatin had at least one serious adverse event of vascular origin (two non-fatal myocardial infarctions, one stroke, 13 ischaemic or other cardiovascular events, and one carotid artery stenosis), compared with 13 controls (12 ischaemic or other cardiovascular events, and one peripheral vascular aneurysm). Other cardiovascular events were mostly angina, chest pain not otherwise specified, or exacerbations of pre-existing congestive heart failure. These serious adverse events of vascular origin have not been adjudicated. No cases of rhabomyolysis or myopathy were noted. The frequency of reported myalgia was 126/752 (17%).

Discussion

Our results showed that the torcetrapib-induced inhibition of CETP was associated with raised HDL cholesterol and lowered LDL cholesterol, changes that would have been expected to be antiatherogenic. However, no significant attenuation of atherosclerosis progression could be identified by measurement of the thickness of carotid intima-media. What is the reason for this discrepancy? Randomised trials of the effects of lipid lowering regimens on thickness of carotid intima media have consistently shown that a reduction in LDL cholesterol attenuates thickening of carotid intima-media. A pooled analysis of several of these trials suggested that a mean reduction in LDL cholesterol of about 20% would translate into a thinning of carotid intima-media by 0·012 mm per year.[33] Thus, even without augmentation of HDL cholesterol, treatment with torcetrapib and atorvastatin would have been expected to attenuate the thickening of carotid intima-media.

Evidence from randomised controlled trials supports the assumption that HDL cholesterol is associated with attenuation of maximum thickness of carotid intima-media. Figure 3 shows the inverse relation between the rate of carotid intima-media thickening and raised HDL cholesterol at the end of randomised controlled trials.[34–42] Our findings for HDL cholesterol in controls fitted on the curve, but the result from the torcetrapib and atorvastatin group was an outlier. One explanation for this deviation might be that the recorded rise in blood pressure in the torcetrapib and atorvastatin group offset the potential benefit of the lipid changes. A meta-analysis of trials on the effect of treatment to lower blood pressure showed that a mean fall of 3·5 mm Hg in systolic pressure reduced carotid intima-media thickening by 0·007 mm per year, which in a linear extrapolation would translate to a 0·011 mm per year difference for a 5·4 mm Hg difference in pressure.[43] Thus, a potential blood pressure effect might counteract the beneficial effect of a reduction in LDL cholesterol, but would probably not have offset the expected effect of a large increase in HDL cholesterol on the carotid intima-media.

	Atorvastatin monotherapy	Atorvastatin plus torcetrapib	p
Baseline data for patients in full analysis set* (n=683)			
Total cholesterol (mmol/L)	4·76 (0·67)	4·78 (0·75)	
LDL-cholesterol (mmol/L)	2·60 (0·49)	2·60 (0·54)	
HDL cholesterol (mmol/L)	1·23 (0·25)	1·23 (0·29)	
Ratio of LDL to HDL cholesterol	2·1 (1·8, 2·5)	2·2 (1·8, 2·5)	
Triglycerides (mmol/L)	1·87 (1·46–2·43)	1·89 (1·50–2·40)	
Randomised patients with baseline blood pressure measurements (n=750)			
Systolic blood pressure (mm Hg)†	119·6 (10·2)†	121·2 (11·1)†	
Diastolic blood pressure (mm Hg)†	74·9 (6·6)†	74·6 (7·1)†	
24-month follow-up data for patients in full analysis set‡ (n=681)			
Total cholesterol (mmol/L)	4·83 (0·77)	5·03 (0·92)	0·004
LDL cholesterol (mmol/L)	2·66 (0·58)	2·17 (0·74)	<0·0001
HDL cholesterol (mmol/L)	1·21 (0·27)	2·00 (0·57)	<0·0001
Ratio of LDL to HDL cholesterol	2·2 (1·9 to 2·6)	1·0 (0·8 to 1·5)	<0·0001§
Triglycerides (mmol/L)	1·87 (1·49 to 2·38)	1·64 (1·21 to 2·29)	0·0005§
Randomised patients with postbaseline blood pressure measurements (n=739)			
Systolic blood pressure (mm Hg)†	121·2 (9·7)†	127·9 (11·2)†	<0·0001
Diastolic blood pressure (mm Hg)†	75·4 (6·0)†	77·1 (7·0)†	<0·0001
Change from baseline			
Total cholesterol	2·3% (0·8)¶	5·9% (0·8)¶	0·002
LDL cholesterol	4·4% (1·5)¶	−13·3% (1·5)¶	<0·0001
HDL cholesterol	−1·8% (1·4)¶	61·6% (1·4)¶	<0·0001
Triglycerides (%)	1·5% (−19·0 to 29·5)	−12·6% (−31·3 to 9·4)	<0·0001‖
Systolic blood pressure (mm Hg)†	1·5 (6·9)†	6·6 (9·2)†	<0·0001**
Diastolic blood pressure (mm Hg)†	0·6 (4·5)†	2·5 (5·0)†	<0·0001**

Data are mean (SD), median (IQR), unless otherwise specified. *Patients who had at least one dose of study drug and had a valid carotid ultrasound study at both baseline and at least one follow-up visit. †Average of all available measurements. ‡A last observation carried forward (LOCF) technique was used to impute 24-month follow-up data. One patient from each group did not have lipid measurements at their final visit. §p value from Wilcoxon rank sum test. ¶Least-square mean percentage change (SE). ‖p value from analysis of covariance on rank transformed data, last observation carried forward. **p value from analysis of covariance on average of all postrandomisation measurements.

Table 3: **Change in selected characteristics between baseline and final visit**

The deviation could also be explained by the possibility that HDL cholesterol particles that accumulate in response to CETP-inhibition do not function normally. However, in cholesterol-fed rabbits, torcetrapib has been shown to inhibit atherosclerosis by means of an increase in HDL cholesterol with only a small change in non-HDL cholesterol in the treated animals.[24] The possibility that proatherogenic HDL particles mediate the response to torcetrapib in treated patients cannot be excluded.

Our findings in mixed dyslipidaemia patients are consistent with the results from the two other torcetrapib imaging trials, which also failed to show a beneficial effect of torceptrapib, either on the progression of coronary atherosclerosis (as assessed by intravascular ultrasound) in coronary heart-disease patients[44] or on carotid intima-media thickening in patients with familial hypercholesterolaemia.[45] The changes in lipid profiles in

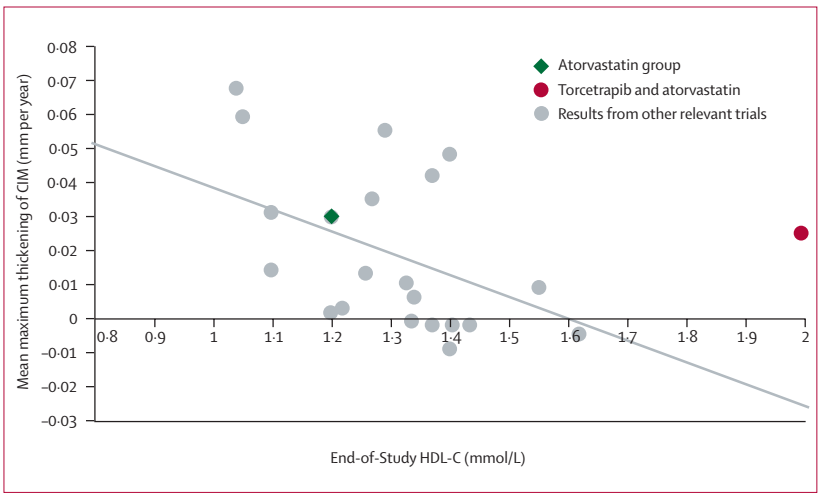

Figure 3: **Randomised controlled trials on the effect of lipid lowering on thickness of carotid intima-media**
Comparison of post-treatment HDL cholesterol with annual mean maximum rate of thickening of carotid intima media (CIM), in randomised controlled trials of the effect of lipid lowering.[34–42] The straight line represents a linear regression analysis of all relevant trials, weighted by study size, and excluding our results (Spearman's rho=−0·60; p=0·003).

these two imaging trials were similar to our findings: torcetrapib was associated with increased HDL cholesterol, reduced LDL cholesterol, and reduced plasma triglyceride. Several hypotheses have been put forward to explain these results—eg, torcetrapib might augment a subclass of HDL particles that do not transport cholesterol in the reverse direction; CETP inhibition might not be antiatherosclerotic in people; or the effect of CETP inhibition on atherosclerosis might depend on baseline CETP activity.[26,46] However, we still need to investigate the mechanisms underlying the findings of the imaging studies. Interactions between certain patient factors (such as sex, metabolic syndrome, and baseline intima-media thickness) and treatment should be interpreted as starting hypotheses for future studies.

The results of the three imaging trials should also be considered in the context of the development programme for torcetrapib and a randomised, double-blind, controlled trial designed to assess the effect of torcetrapib and atorvastatin, compared with atorvastatin alone, on cardiovascular morbidity and mortality.[25] This trial was prematurely stopped after a median follow-up of 18 months, because of a significant excess of total mortality in patients given torcetrapib and atorvastatin. The three imaging studies all showed more cardiovascular adverse events in the torcetrapib and atorvastatin groups than in patients given atavorstatin alone.[45,47] However, for the carotid intima-media thickening trials, these events have not been adjudicated. Furthermore, none of these imaging studies was powered to study differences in vascular events between treatment arms. Yet, the absence of benefit in the three imaging trials can be seen as consistent with the excess mortality in the terminated trial.[25] The fact that none of the imaging trials showed that combined treatment with torcetrapib and atorvastatin produced adverse effects on progression of atherosclerosis raises the possibility that torcetrapib might have a serious adverse effect that is unrelated to its CETP-inhibiting activity. If so, CETP inhibition as a strategy to inhibit atherosclerosis might have a future, dependent on the results of continued studies to investigate the findings of trials to-date.

The imaging trials that investigated the effect of torcetrapib on the progression of coronary and carotid atherosclerosis all showed neutral results on their primary endpoints, and an indication of harm was suggested in the common carotid secondary endpoint in the one previous carotid ultrasound study.[26,45] In the context of the harm identified in the most recent trial, these results suggest that carotid intima-media thickness is a very powerful marker of clinical benefit, since it provides an integrated measure of cardiovascular risk.[27] However, imaging mainly measures effectiveness, whereas long-term outcome trials measure both effectiveness and overall safety; therefore, both contribute valuable information during the drug development process, and neither is a substitute for the other.

Limitations of our study include the fact that slightly more than 20% of participants did not continue the study; however, the power of the study was not affected by dropouts, since B-mode ultrasound scans obtained at 6, 12, and 18 months after baseline permitted calculation of a rate of change in carotid intima-media thickness for each treatment group. Second, although our mean follow-up was short, we can speculate that a longer study duration would not have increased our ability to detect differences between groups, since no effect could be identified within 2 years.

Contributors
CLS, WAR, JHR, JJPK, DEG, GWE, WTD, and MLB participated in the concept and design of the study. FLJV, CLS, WAR, JHR, JJPK, DEG, MLB, RMV, and GWE acquired data and drafted the report. FLJV, CLS, WAR, JHR, JJPK, DEG, GWE, MLB, RMV, and CHT participated in the interpretation of data and critical revision of the paper. WTD did statistical analyses of the data. CLS, WAR, JHR, JJPK, and GWE supervised the paper.

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Conflict of interest statement

MLB has received grants for studies on carotid intima-media thickness, honoraria for professional input regarding issues on carotid intima-media thickness, or both, from Astra-Zeneca, Icelandic Heart Foundation, Organon, Pfizer, Netherlands Heart Foundation, Netherlands Organisation for Health Research and Development, Servier, and Unilever. FLJV has received research grants from Merck, and Netherlands Organisation for Health Research and Development. GWE has received honoraria, consulting fees, and grant support for professional input on CIMT issues from Astra-Zeneca, Organon, and Pfizer. WAR has received research contracts from Astra-Zeneca, Organon, and Pfizer. DEG has received grant support from, and delivered lectures for, Pfizer, Astra-Zeneca, Organon, Servier, and Merck. JJPK has received research grant support from Pfizer. RMV has had a contract as a study investigator with Pfizer, and has periodically received honoraria from Pfizer for lectures. CHT has no conflicts of interest. JHR, CLS, and WTD are employees of, and CLS and WTD are shareholders of, Pfizer.

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