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COMMENTARY

The failure of torcetrapib: what have we learned?

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The failure of the cholesterol ester transfer protein (CETP) inhibitor, torcetrapib, has led to questions regarding whether the molecule itself or the mechanism of CETP inhibition was responsible for the adverse cardiovascular outcomes. Given the association with increases in blood pressure and plasma aldosterone levels, torcetrapib has been postulated to have adverse 'off-target' effects. In this issue of British Journal of Pharmacology, Forrest and co-workers have elegantly investigated these effects, demonstrating two salient points—(1) the pressor effect of torcetrapib is independent of CETP inhibition and (2) although associated with hyperaldosteronism, the pressor effect is likely not mediated by hyperaldosteronism. Anacetrapib, by contrast, did not demonstrate any pressor or off-target effects. Despite these findings, it remains to be proven whether the adverse cardiovascular outcomes from torcetrapib were indeed related to the pressor effects and whether CETP inhibition by other agents will result in beneficial clinical outcomes. Yet, the studies of Forrest and co-workers do bring us closer to unravelling the reasons behind the failure of torcetrapib.
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Reductions in low-density lipoprotein cholesterol (LDL-C) through the use of anti-dyslipidemic drugs, primarily statins, have decreased cardiovascular morbidity and mortality by approximately 25%. However, cardiovascular disease continues to be a leading cause of death and lost productivity. As epidemiologic data have identified a strong inverse relation between high-density lipoprotein cholesterol (HDL-C) levels and coronary heart disease, the development and investigation of therapies focused on raising HDL-C levels have recently been undertaken.

Cholesterol-laden macrophages ('foam cells') are critical to atheroma formation, with the inherent opposing process being the movement of cholesterol from these foam cells to the liver for biliary excretion—a process called reverse cholesterol transport (RCT). Although proposed anti-atherogenic properties of HDL include anti-inflammatory, antithrombogenic and endovascular effects, RCT is considered to be the primary mechanism by which HDL exerts its anti-atherogenic effects. RCT, however, is a complex process, requiring the concerted efforts of several different enzymes, organs and molecules. Key areas in the pathway include production of apolipoprotein (apo) A-I with mobilization of cholesterol from the periphery on HDL particles, transformation of the HDL particles themselves and catabolism of HDL lipid content.

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A salient step in the transformation of HDL particles during RCT is mediated by cholesterol ester transport protein (CETP), which exchanges triglycerides from apo-B-containing lipoproteins (low-density lipoprotein and very-low-density lipoproteins) for cholesteryl esters on HDL. CETP was recognized as a potential anti-atherosclerotic target when patients with decreased CETP activity due to *CETP* mutations seemed to have elevated HDL levels (Inazu *et al.*, 1990). Consequently, interest arose into the pharmaceutical development of CETP inhibitors, such as JTT-705/Roche R1658 (Basel, Switzerland), torcetrapib, and anacetrapib.

Early studies with CETP inhibitors showed promising results with significant increases in HDL-C levels and reduced progression of atherosclerosis in animal models (Okamoto *et al.*, 2000). However, initial phase 2 trials with torcetrapib revealed mean increases of 1.3–2.2 mm Hg in systolic blood pressure (SBP) and 0.9–1.1 mm Hg in diastolic blood pressure at doses of 60 or 90 mg per day with 4% of individuals experiencing a >15 mm Hg SBP increase (Tall *et al.*, 2007). Consequently, the dose of torcetrapib was restricted to 60 mg daily. Three phase 3 trials using torcetrapib (60 mg daily) with atorvastatin vs atorvastatin alone to evaluate surrogate coronary heart disease endpoints of carotid intima-media thickness or intravascular atherosclerosis were, in fact, disappointing regardless of the significant approximately 50% increase in HDL-C and approximately 20% decrease in LDL-C effected by torcetrapib. Moreover, despite the dose restriction in these trials, mean SBP increased by 2.8–5.4 mm Hg, with 5–9% of individuals developing a >15 mm Hg increase (Bots *et al.*, 2007; Kastelein *et al.*, 2007; Nissen *et al.*, 2007). In late 2006,

all torcetrapib trials were ceased due to the interim findings of the ILLUMINATE (Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events) trial, in which 15 067 individuals at high risk for coronary heart disease were randomized to treatment with atorvastatin (10–80 mg per day) + placebo or atorvastatin + torcetrapib (60 mg per day). Compared to those in the atorvastatin alone arm, individuals in the torcetrapib arm demonstrated an increased risk of cardiovascular events despite a 72% increase in HDL-C and 25% decrease in LDL-C levels (Barter *et al*., 2007). These surprising results led to speculation that either the mechanism of CETP inhibition or the torcetrapib molecule itself was at fault, and that HDL-C raising for atherogenesis prevention may, in fact, be a futile strategy.

Although the cause for the increased SBP by torcetrapib remains unknown, it has been attributed to some unknown generalized vascular 'off-target' drug effect, such as calcium-mediated vasospasm or hyperaldosteronism. In fact, *post hoc* analysis of the results of ILLUMINATE revealed increased aldosterone levels in the torcetrapib arm, although a direct comparison of the mean values was not possible due to only 87–88% of samples being analysed and 53–57% of samples having aldosterone levels below the lower limit of quantification (Barter *et al*., 2007). Thus, conclusive results regarding a causal relation between hyperaldosteronism and increased SBP by torcetrapib were not possible in ILLUMINATE. But, the findings that adverse blood pressure effects were not observed in studies evaluating two other CETP inhibitors—anacetrapib and JTT-705/R1658 (Kuivenhoven *et al*., 2005; Krishna *et al*., 2007)—lend circumstantial evidence that the torcetrapib molecule and not necessarily the CETP inhibition mechanism was likely responsible.

The study by Forrest *et al*. (2008) in this issue of British Journal of Pharmacology specifically sought to evaluate the off-target effects of torcetrapib (Forrest *et al*., 2008). The authors also evaluated whether these same off-target effects were present in an alternate CETP inhibitor, namely anacetrapib. In a series of elegant experiments, the authors demonstrated that infusion of torcetrapib but not anacetrapib resulted in acute increases in blood pressure in both normal mice (naturally lacking CETP) and in transgenic mice with simian CETP, indicating that the blood pressure elevations are mediated through a CETP-independent pathway. The discrepancy in pressor effects with torcetrapib vs anacetrapib was confirmed in other animal models. Interestingly, torcetrapib did not exert a direct contractile effect on vascular smooth muscle, nor did it increase blood pressure through central, sympathetic nervous system, angiotensin type 1 or endothelin receptor effects. Instead, torcetrapib was associated with an approximately 2-fold and 3.5-fold increase in plasma levels of aldosterone and corticosterone, respectively. Conversely, anacetrapib did not demonstrate any significant changes in these adrenal steroid levels. Use of trilostane, a 3β-hydroxysteroid dehydrogenase inhibitor, did not block the increase in blood pressure by torcetrapib despite inhibiting the increases in plasma aldosterone and corticosterone levels. Similarly, use of the mineralocorticoid receptor antagonist epleronone also did not inhibit the pressor effect of torcetrapib. However, torcetrapib but not anacetrapib increased aldosterone release through a direct action on adrenocortical cells and more importantly, torcetrapib did not increase blood pressure in acutely adrenalectomized rodents. These latter two findings signify that the adrenals are indeed somehow related to the pressor effects of torcetrapib. Thus, the studies by Forrest *et al*. (2008) provide two main conclusions regarding the pressor effect of torcetrapib: (1) it occurs independent of CETP inhibition; and (2) it is not likely mediated by aldosterone or corticosterone despite associated increased aldosterone and corticosterone levels with torcetrapib administration.

Although the studies by Forrest *et al*. (2008) rule out several possible explanations for the pressor effect of torcetrapib, they do not determine the actual cause of increased blood pressure. All that is known is that adrenalectomy obviates the pressor effect of torcetrapib whereas inhibition of the sympathetic nervous system or the early steps of adrenal steroid synthesis do not. Even aberrant action at the mineralocorticoid receptor does not seem to be a player as the pressor effect of torcetrapib was unaffected by epleronone. Thus, one possibility is that the rise in corticosterone and aldosterone levels may be a red herring. There may be, as of yet, unknown hormonal pathways that influence blood pressure or the increase in SBP is mediated through earlier hormones in the adrenal synthesis pathway such as pregnenlone. More importantly, it remains to be determined whether the pressor effect rather than some other mechanism led to the increased cardiovascular outcomes with torcetrapib. For example, even though it seems unlikely, based on the results of Forrest *et al*. (2008), that elevated aldosterone levels are causative of the pressor effect, the studies presented did not evaluate whether hyperaldosteronism itself is related to increased atherosclerosis. To evaluate this hypothesis would require examination of the atherosclerotic lesions among animals treated with torcetrapib and trilostene vs torcetrapib alone. Similarly, whether CETP inhibition is indeed a beneficial strategy for atherosclerosis prevention remains to be determined.

The caveat for all strategies aimed at raising HDL-C is that the quality and not the quantity of HDL particles is most important for atherosclerosis prevention. For example, HDL can be transformed into pro-atherogenic particles under certain situations such as inflammation, and certain subclasses of HDL correlate better with anti-atherogenic effects (Joy and Hegele, 2008). Although the RCT process is becoming better understood, the most critical aspects of RCT for HDL-raising remain unknown. It is important to recognize that inhibition of CETP may have mixed pro-atherogenic and anti-atherogenic effects (Joy and Hegele, 2008). On the one hand, inhibiting CETP would inhibit the movement of cholesteryl esters onto apo-B-containing lipoproteins and thereby, potentially decrease the cholesteryl esters-laden LDL available for uptake by macrophages for foam cell formation (an anti-atherogenic effect). Conversely, inhibiting this HDL 'remodeling' process may diminish apo A-I and lipid-poor HDL stores available for peripheral cholesterol efflux or may decrease the possibility of cholesteryl esters being transferred to apo-B-containing lipoproteins for excretion by the liver (a pro-atherogenic

effect). Currently, normal CETP works to maintain a balance between these opposing outcomes. But, gauging the ability of CETP inhibitors to tweak the balance in favour of anti-atherogenic outcomes requires clinical outcomes trials. The results of Forrest *et al*. (2008) illuminate some of the off-target effects of torcetrapib, and reassure us that these effects are not present with anacetrapib. However, learning from the failure of torcetrapib, we must remain cautious in accepting promising results from surrogate end-point trials, and instead patiently await the results of clinical outcomes trials of HDL-raising strategies.

References

Barter PJ, Caulfield M, Eriksson M, Grundy SM, Kastelein JJ, Komajda M *et al*. (2007). Effects of torcetrapib in patients at high risk for coronary events. *N Engl J Med* **357**: 2109–2122.

Bots ML, Visseren FL, Evans GW, Riley WA, Revkin JH, Tegeler CH *et al*. (2007). Torcetrapib and carotid intima-media thickness in mixed dyslipidaemia (RADIANCE 2 study): a randomised, double-blind trial. *Lancet* **370**: 153–160.

Forrest MJ, Bloomfield D, Briscoe RJ, Brown PN, Cumiskey A-M, Ehrhart J *et al*. (2008). Torcetrapib-induced blood pressure elevation is independent of CETP inhibition and is accompanied by increased circulating levels of aldosterone. *Br J Pharmacol* **154**: 1465–1473 (this issue).

Inazu A, Brown ML, Hesler CB, Agellon LB, Koizumi J, Takata K *et al*. (1990). Increased high-density lipoprotein levels caused by a common cholesteryl-ester transfer protein gene mutation. *N Engl J Med* **323**: 1234–1238.

Joy T, Hegele RA (2008). Is raising HDL a futile strategy for atheroprotection? *Nat Rev Drug Discov* **7**: 143–155.

Kastelein JJ, van Leuven SI, Burgess L, Evans GW, Kuivenhoven JA, Barter PJ *et al*. (2007). Effect of torcetrapib on carotid atherosclerosis in familial hypercholesterolemia. *N Engl J Med* **356**: 1620–1630.

Krishna R, Anderson MS, Bergman AJ, Jin B, Fallon M, Cote J *et al*. (2007). Effect of the cholesteryl ester transfer protein inhibitor, anacetrapib, on lipoproteins in patients with dyslipidaemia and on 24-h ambulatory blood pressure in healthy individuals: two double-blind, randomised placebo-controlled phase I studies. *Lancet* **370**: 1907–1914.

Kuivenhoven JA, de Grooth GJ, Kawamura H, Klerkx AH, Wilhelm F, Trip MD *et al*. (2005). Effectiveness of inhibition of cholesteryl ester transfer protein by JTT-705 in combination with pravastatin in type II dyslipidemia. *Am J Cardiol* **95**: 1085–1088.

Nissen SE, Tardif JC, Nicholls SJ, Revkin JH, Shear CL, Duggan WT *et al*. (2007). Effect of torcetrapib on the progression of coronary atherosclerosis. *N Engl J Med* **356**: 1304–1316.

Okamoto H, Yonemori F, Wakitani K, Minowa T, Maeda K, Shinkai H (2000). A cholesteryl ester transfer protein inhibitor attenuates atherosclerosis in rabbits. *Nature* **406**: 203–207.

Tall AR, Yvan-Charvet L, Wang N (2007). The failure of torcetrapib: was it the molecule or the mechanism? *Arterioscler Thromb Vasc Biol* **27**: 257–260.