

The future of CETP inhibition – still to be REVEALed

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In this issue (see pages 126–33), Paul Durrington has written an excellent review of one of the most interesting conundrums in current clinical lipidology – the putative role of cholesteryl ester transfer protein (CETP) inhibitors.

Reducing the residual cardiovascular risk that remains after statin use is a frontline challenge for preventive cardiology. After attention to other modifiable risk factors, further reduction of low-density lipoprotein cholesterol (LDL-C) levels and increasing high-density lipoprotein cholesterol (HDL-C) levels are under particular scrutiny.^{1,2} The cardioprotective epidemiology of HDL-C is strong and well known, and so it often comes as a shock to health professionals that there is no direct proof that raising HDL-C improves cardiovascular outcomes. Despite this, raising HDL-C remains an attractive potential approach for tackling residual risk as many patients already achieve very low LDL-C levels on treatment and even at these low levels, HDL-C still predicts cardiovascular outcomes.³

Levels of complexity

High-density lipoproteins are complex lipoproteins about which much remains to be understood. Their diverse protein content and multiple structures and functions suggest a number of potential mechanisms by which they may offer protection against cardiovascular disease. What has become clear though, is that simple measurement of the level of HDL-C is not a determinant of its functional capacity and the pressure is on to find a measure that is.⁴

CETP inhibitors raise HDL-C levels by inhibiting the transfer of cholesterol ester from HDL to larger lipoproteins such as chylomicrons, very-low-density lipoprotein (VLDL) and LDL. The experience of the first in class, torcetrapib, is well known, as the ILLUMINATE study was terminated early due to an excess of deaths in the treatment group.⁵ Subsequent investigations suggested that torcetrapib has an off-target hypertensive effect but this in itself may not be enough to explain all the deaths. As a result, the development of additional CETP inhibitors has been cautious but neither dalcetrapib,

anacetrapib nor evacetrapib have, as yet, shown apparent off-target side effects.

Trial failure

On 7th May, a trial (Dal-OUTCOMES) investigating the safety and efficacy of dalcetrapib in stable coronary heart disease (CHD) patients on a statin was terminated a year early by its data and safety monitoring board as no clinical benefit was becoming apparent. As a result, the development programme of dalcetrapib has been halted. Compared with anacetrapib and evacetrapib, dalcetrapib is a weaker CETP inhibitor with smaller effects on HDL-C and almost no effect on LDL-C. Its advantage was thought to lie in the fact that its inhibition fell short of attenuating CETP-mediated HDL remodelling, thereby encouraging the formation of pre- β HDL thought to be important as a cholesterol acceptor from peripheral tissues.⁶ For some, the trial cessation was not unexpected as surrogate trials on brachial artery reactivity (as an index of endothelial function) and plaque imaging had been, respectively, negative and neutral.^{7,8}

There are theoretical reasons why CETP inhibitors may not deliver their promise and this underlines the need for properly conducted clinical outcome trials. As Professor Durrington explains, CETP contributes to reverse cholesterol transport, as some of the cholesterol accepted from HDL is taken up by the liver by LDL or chylomicron remnant receptors. Interfering with this may be pro-atherogenic, especially if conventional reverse cholesterol transport via the scavenger receptor class B1 (SR-B1) receptor in the liver is saturated. It is also possible that the enlarged HDL particles derived through CETP inhibition may be dysfunctional, although *in vitro* experiments with HDL derived from torcetrapib in the ILLUMINATE trial did show increased cellular cholesterol efflux.⁹ In addition, adverse effects on nitric oxide stimulation, endothelin-1 secretion, apolipoprotein A-1 modification and innate immunity have all been proposed.

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Patients with gastritis, esophagitis, or gastroesophageal reflux consider 220 mg taken as one 110 mg capsule twice daily due to the elevated risk of major gastro-intestinal bleeding. **Renal impairment:** contraindicated in severe renal impairment (CrCl < 30 mL/min); patients with renal impairment and a high risk of bleeding consider 220 mg taken as one 110 mg capsule twice daily. Close clinical surveillance is recommended in patients with renal impairment. As above assess renal function prior to initiation to exclude patients with severe renal impairment and assess renal function at least once a year or more frequently as needed. Concomitant verapamil 220 mg taken as one 110 mg capsule twice daily; Pradaxa and verapamil should be taken at the same time. No dose adjustment required but close clinical surveillance in patients < 50 kg. Not recommended if liver enzymes > 2 Upper Limit of Normal (ULN). If switching from Pradaxa to parenteral anticoagulant wait 12 hours after the last dose of Pradaxa; if switching from parenteral anticoagulants to Pradaxa then Pradaxa should be given 0–2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment; if switching from Pradaxa to VKA adjust the starting time of the VKA based on CrCl; if switching from VKA to Pradaxa stop VKA and give Pradaxa once INR < 2.0. Cardioversion patients can stay on Pradaxa whilst being cardioverted. Not recommended aged < 18 years. Pradaxa should be swallowed whole with water, with or without food. 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Haemorrhagic risk: Close clinical surveillance (signs of bleeding or anaemia) is recommended throughout the treatment period, especially when haemorrhagic risk is increased or risk factors combined. Factors which may increase haemorrhagic risk: age ≥ 75 years; moderate renal impairment (CrCl 30–50 mL/min); P-glycoprotein inhibitor co-medication; body weight < 50 kg; acetylsalicylic acid (aspirin); NSAID; cyclosporin; selective serotonin re-uptake inhibitors (SSRIs) or selective serotonin norepinephrine re-uptake inhibitors (SNRIs); other drugs which may impair haemostasis; diseases/procedures associated with a risk of bleeding such as coagulation disorders, thrombocytopenia or functional platelet defects, recent biopsy, major trauma, bacterial endocarditis, esophagitis, gastritis or gastroesophageal reflux. The measurement of dabigatran related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors. Patients who develop acute renal failure must discontinue Pradaxa. If severe bleeding occurs, discontinue treatment and investigate the source of the bleeding. Avoid or use with caution agents which may increase the risk of haemorrhage: use of fibrinolytic agents for the treatment of acute ischaemic stroke may be considered if the patient presents with a dTT, ECT or aPTT not exceeding the ULN according to the local reference range. Avoid concomitant administration with P-gp inducers. Patients on dabigatran etexilate who undergo surgery or invasive procedures are at increased risk for bleeding therefore surgical interventions may require the temporary discontinuation of dabigatran etexilate; prescribers should consult the Summary of Product Characteristics for further information. Procedures such as spinal anaesthesia may require complete haemostatic function. The risk of spinal or epidural haematoma may be increased in cases of traumatic or repeated puncture and by the prolonged use of epidural catheters. After removal of a catheter, an interval of at least 2 hours should elapse before the administration of the first dose of dabigatran etexilate; these patients require observation for neurological signs and symptoms of spinal or epidural haematoma. Treat with caution patients at high surgical mortality risk and with intrinsic risk factors for thromboembolic events. Myocardial infarction. Contains Sunset Yellow (E110) which may cause allergic reactions. **Interactions:** Anticoagulants and antiplatelet aggregation agents; Strong P-gp inhibitors e.g. amiodarone, quinidine, verapamil, clarithromycin co-administration (close clinical surveillance); verapamil co-administration - reduce Pradaxa dose to 220 mg (see above); not recommended for concomitant treatment posaconazole, dronedarone, protease inhibitors including ritonavir and its combinations with other protease inhibitors; avoid with P-gp inducers e.g. rifampicin, St John's wort, carbamazepine, phenytoin; SSRIs or SNRIs. Dabigatran etexilate and dabigatran are not metabolized by cytochrome CYP450 system, therefore related medicinal product interactions not expected. Pantoprazole and other proton-pump inhibitors (PPI) were co-administered with Pradaxa in clinical trials and concomitant PPI treatment did not appear to reduce the efficacy of Pradaxa. Ranitidine administration together with Pradaxa had no clinically relevant effect on the extent of absorption of dabigatran. **Fertility, pregnancy and lactation:** Avoid pregnancy during treatment. Do not use in pregnancy unless clearly necessary. Discontinue breast-feeding during treatment. **Undesirable effects:** Most commonly reported adverse reactions are bleedings occurring in total in approximately 16.5 % in patients with atrial fibrillation treated for the prevention of stroke and SEE. Common (≥ 1/100, < 1/10): anaemia; epistaxis; gastrointestinal haemorrhage; abdominal pain; diarrhoea; dyspepsia; nausea; hepatic function abnormal/liver function test abnormal; genitourinary haemorrhage (150 mg). Prescribers should consult the Summary of Product Characteristics for further information on side effects. **Pack sizes and NHS price:** 110 mg 60 capsules £65.90 150 mg 60 capsules £66.90. **Legal category POM MA numbers:** 110 mg EU/1/09/442/007 (60 capsules) 150 mg EU/1/09/442/011 (60 capsules) **Marketing Authorisation Holder:** Boehringer Ingelheim International GmbH, Binger Str. 173, D-55216 Ingelheim am Rhein, Germany. Prescribers should consult the Summary of Product Characteristics for full prescribing information. **Prepared in July 2012.**

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Boehringer Ingelheim Drug Safety on 0800 328 1827 (toll-free).

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Continued development

At present, both anacetrapib and evacetrapib are continuing their development. These high-intensity CETP inhibitors can both deliver HDL-C elevations in excess of 130% and LDL-C reductions of around 40%. Remarkably, these changes still occur despite background statin use. The HPS3 TIMI 55 REVEAL trial, run by Oxford University, is investigating the effects of anacetrapib in addition to atorvastatin in over 30,000 people with atherosclerotic vascular disease over a four-year period. Given the large reduction in LDL-C induced by additional anacetrapib, it is hard to imagine this trial will not be positive when it reports in 2017. The contribution of the increased level of HDL-C, however, may still be difficult to quantify.

Winston Churchill once described Russia as “a riddle wrapped in a mystery inside an enigma”. The same can be said of CETP inhibition, the difference being that proper clinical investigation will unlock the puzzle and potentially herald a major new era in residual risk reduction ●

Conflict of interest

None declared.

Editors' note

See also the article by Professor Paul Durrington on pages 126–33 of this issue.

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