DECADE IN REVIEW—DYSLIPIDAEMIA

Resurgence of targets and compounds to treat dyslipidaemia

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Over the past decade, we have witnessed the unparalleled success of statins to treat dyslipidaemia. Target identification by Mendelian randomization, human monoclonal antibodies, gene therapy, RNA-based targets, and atherogenic lipoproteins other than LDL cholesterol have fuelled intense development efforts that might bear fruit in the very near future.

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When Terje Pedersen first presented the results of the Scandinavian Simvastatin Survival Study at the AHA Scientific Sessions on 16 November 1994 in Dallas, TX, USA, he probably did not realize that the study would initiate a global revolution in statin therapy. Today, statins are the most widely prescribed class of drugs, and although the results of this study were presented 20 years ago, no other drug has since been shown to have any additional benefit for patients with dyslipidaemia. Inhibitors of phospholipases, cholesteryl ester transfer protein (CETP), and cholesterol absorption, as well as agonists of peroxisome proliferator-activated receptor, thyroxin receptor, and nicotinic acid have either been toxic or not provided a beneficial outcome for patients. However, not all discoveries in the past decade for the therapeutic control of dyslipidaemia can be claimed by statins. In 2003, Boileau and colleagues mapped a locus associated with familial hypercholesterolaemia in the gene encoding proprotein convertase subtilisin/kexin type 9 (PCSK9). As with the Scandinavian Simvastatin Survival Study, Boileau *et al.* could not have foreseen that their discovery would develop into the currently most exciting class of lipid-lowering drugs—monoclonal antibodies against circulating PCSK9. These two discoveries have led to an unprecedented number of developments in the field of dyslipidaemia in the past decade.

In 2004, the authors of two papers first established the clinical importance of statins in the treatment of cardiovascular disease, which turned the hypothesis that 'lower LDL cholesterol is better' into a core principle. In the PROVE-IT study,[1] Cannon and co-workers convincingly demonstrated that 80 mg of atorvastatin was superior to 40 mg of pravastatin in outcome parameters including death, myocardial infarction, unstable angina, and revascularization (a 16% risk reduction in favour or atorvastatin; $P = 0.005$), when administered shortly after an acute coronary syndrome (ACS).[1] This study transformed care for patients with ACS; 80 mg of atorvastatin straight after an ACS episode has now become routine clinical practice in coronary care units in most countries. This strategy has saved innumerable lives of patients with coronary artery disease (CAD) and protected them against recurrent events.

In the TNT study,[2] also published in 2004, LaRosa and colleagues demonstrated that 80 mg was superior to 10 mg of atorvastatin for treating patients with stable CAD. High-dose atorvastatin reduced the primary end point (occurrence of a major cardiovascular event) by 22% compared with the lower dose of the drug ($P < 0.001$).[2] This study has also enabled many secondary analyses that aid our understanding of renal function during statin therapy, the clinical safety of low LDL-cholesterol levels, and that a reduction in adverse clinical outcomes is independent of almost any baseline patient characteristic, including LDL-cholesterol level itself. These 'statin principles' were extended into the realm of primary prevention in 2008 in the JUPITER trial.[3] Ridker *et al.* selected patients with an elevated C-reactive protein level (measured by high-sensitivity assay), but who were free from CAD, and demonstrated that a daily dose of 20 mg rosuvastatin robustly reduced the incidence of major adverse cardiovascular events by 44% compared with placebo ($P < 0.00001$).[3] Again, efficacy was observed in all subgroups, including men and women, the elderly and young, tobacco smokers and nonsmokers, and those with or without metabolic syndrome. More importantly, the JUPITER trial[3] results highlighted the link between inflammation, dyslipidaemia, and atherosclerotic vascular disease, which has led to the current development of selective anti-inflammatory strategies in outcome trials by the same research group.

In two papers published in 2006 and 2008, respectively, investigators applied advanced molecular biology techniques to the study of lipid control.[4,5] In the first study, mRNA inhibition by subcutaneously administered small oligonucleotides against apolipoprotein B-100 (apoB-100) lowered the levels of all atherogenic lipoproteins in human volunteers with mild dyslipidaemia.[4] These results have led to the development of small inhibitory RNAs, mRNA inhibitors, and locked nucleic acid inhibitors that target angiopoietin-related protein 3, apoB-100, apolipoprotein C-III (apoC-III), apolipoprotein(a) [apo(a)], and PCSK9, and which have all reached phase I and further clinical studies. These developments are just the beginning, and many more will come in the next decade. In the second paper, which garnered little attention when first published, Stroes and colleagues performed the first proof-of-concept study of gene therapy for dyslipidaemia. Alipogene tiparvovec increases the removal of postprandial chylomicrons, the particles known to cause the acute and potentially lethal haemorrhagic pancreatitis associated with the chylomicronaemia syndrome. Alipogene tiparvovec (commercially known as Glybera®; UniQure, Netherlands) became the first gene therapy product to be approved for any indication in the Western world.[5]

Many developments since 1994 have revolved around the biology, pathology, and therapeutic lowering of LDL-cholesterol levels. Only after a number of international

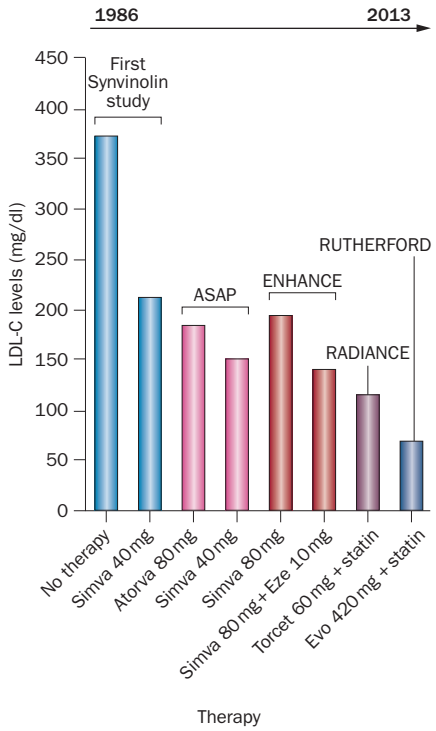

Figure 1 | LDL-cholesterol levels achieved by lipid-lowering therapies developed during the past 3 decades in patients with familial hypercholesterolaemia. Dosing frequencies are per day unless otherwise stated. Abbreviations: Atorva, atorvastatixn; Evo, evolocumab; Eze, ezetimibe; LDL-C, LDL-cholesterol; Simva, simvastatin; Torcet, torcetrapib.

consortia performed large Mendelian randomization studies was the link made between CAD and apo(a), triglyceride-rich lipoproteins, and remnant cholesterol.[6,7] These observations are seminal for our understanding of atherogenesis and initiated an international effort to identify novel strategies to decrease circulating levels of these lipoproteins. Moreover, the results of these Mendelian randomization studies, such as those performed by Nordestgaard[6] and Kathiresan,[7] have questioned the relationship between HDL cholesterol and CAD, which might explain the disappointing results of strategies that raise HDL-cholesterol levels. By contrast, Mendelian randomization and intervention studies have both validated the role of lowering LDL-cholesterol levels to treat dyslipidaemia. Consequently, the discoveries by investigators that CETP, triglyceride-rich lipoproteins, and apo(a) are indeed involved in atherogenesis have led to a search for compounds to safely lower the levels of these proteins, as well as those of apoC-III and, of course, PCSK9. Mendelian randomization studies are now an integral approach in the development of drugs to treat dyslipidaemia.

Of all the developments over the past decade, a paper by Stein and colleagues in 2012 deserves the title of 'game changer'. In this study, a monoclonal antibody against PCSK9 (alirocumab), reduced the relative LDL-cholesterol level by >60% in both volunteers with normal lipid levels and patients with familial hypercholesterolaemia.[8] The excellent safety profile of this drug class has been a relief for clinicians, especially given the previous toxicity-related failures of other compounds. Similar results were obtained in studies with bococizumab and evolocumab, and all three monoclonal antibodies targeted against PCSK9 are already in advanced, phase III outcome trials. Only 9 years have passed between Boileau and colleagues' initial PCSK9 discovery and Stein and co-workers' 2012 paper. This rapid development has been made possible by recombinant DNA and antibody technology. Compared with the >25 years between cloning of the lipoprotein lipase (LPL) gene and the LPL gene therapy trial by our own group, the development of PCSK9-based technologies has been a remarkable achievement.

However, for which patients is the discovery of PCSK9 monoclonal antibodies most beneficial in the short term? To have personally witnessed the ever-decreasing LDL-cholesterol levels that different therapies have achieved in patients with familial hypercholesterolaemia has been immensely gratifying. Between the first simvastatin trial in 1986 and the RUTHERFORD study of evolocumab just last year, a steady decrease in LDL-cholesterol levels from 9.6 mmol/l (371 mg/dl) to ~1.7 mmol/l (65 mg/dl) has been achieved (Figure 1). The discovery that monoclonal antibodies against PCSK9 can lower LDL-cholesterol levels to such an extent has essentially cured familial hypercholesterolaemia; in fact, the LDL-cholesterol levels achieved in these patients are now lower than in the general population. Who would have had the temerity to predict that in 2003?

The final discovery that I would like to highlight was reported in two papers in which triglyceride-rich lipoprotein and remnant cholesterol levels were causally linked to apoC-III and CAD.[9,10] ApoC-III was first hypothesized to reduce triglyceride levels and contribute to the risk of CAD, and on that basis a mRNA inhibitor of apoC-III was developed. These two papers strengthen the association between apoC-III, triglyceride metabolism, and CAD risk.[9,10] The fact that the apoC-III inhibitor is already in clinical development is, therefore, timely and fortuitous. With all of these results comes the hope that novel small-molecule compounds, monoclonal antibodies, and RNA technology will transform dyslipidaemia treatment in the coming decade, for a second time since 1994. We might finally be able to eliminate dyslipidaemia and subsequent atherosclerotic vascular disease for our patients in the very near future.

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Competing interests
J.J.P.K. declares that he has acted as a consultant and received honouraria from the following companies: Aegerion, Amgen, AstraZeneca, Atheronova, Boehringer Ingelheim, Catabasis, Cerenis, CSL Behring, Dezima Pharmaceuticals, Eli Lilly, Esperion, Genzyme, Isis, Merck, Novartis, Omthera, Pronova, Regeneron, Sanofi, The Medicines Company, UniQure, and Vascular Biogenics.

1. Cannon, C. P. *et al.* Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N. Engl. J. Med.* **350**, 1495–1504 (2004).
2. LaRosa, J. C. *et al.* Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N. Engl. J. Med.* **352**, 1425–1435 (2005).
3. Ridker, P. M. *et al.* Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N. Engl. J. Med.* **359**, 2195–2207 (2008).
4. Kastelein, J. J. P. *et al.* Potent reduction of apolipoprotein B and low-density lipoprotein cholesterol by short-term administration of an antisense inhibitor of apolipoprotein B. *Circulation* **114**, 1729–1735 (2006).
5. Stroes, E. S. *et al.* Intramuscular administration of AAV1-lipoprotein lipase S447X lowers triglycerides in lipoprotein lipase-deficient patients. *Arterioscler. Thromb. Vasc. Biol.* **28**, 2303–2304 (2008).
6. Kamstrup, P. R., Tybjærg-Hansen, A., Steffensen, R. & Nordestgaard, B. G. Genetically elevated lipoprotein(a) and increased risk of myocardial infarction. *JAMA* **301**, 2331–2339 (2009).
7. Do, R. *et al.* Common variants associated with plasma triglycerides and risk for coronary artery disease. *Nat. Genet.* **45**, 1345–1352 (2013).
8. Stein, E. A. *et al.* Effect of a monoclonal antibodies to PCSK9 on LDL cholesterol. *N. Engl. J. Med.* **366**, 1108–1118 (2012).
9. Jørgensen, A. B., Frikke-Schmidt, R., Nordestgaard, B. G. & Tybjærg-Hansen, A. Loss-of-function mutations in *APOC3* and risk of ischemic vascular disease. *N. Engl. J. Med.* **371**, 32–41 (2014).
10. The TG and HDL Group of the Exome Sequencing Project, National, Heart, Lung, and Blood Institute. Loss-of-function mutations in *APOC3*, triglycerides, and coronary heart disease. *N. Engl. J. Med.* **371**, 22–31 (2014).