

Sometimes old and inexpensive drugs are nevertheless good drugs, and sometimes improvements in medical practice can reinvigorate old drugs. Despite its mechanistic disadvantages, this might be the case with heparin. Unless new trial data to the contrary with bivalirudin become available, the findings of this meta-analysis³ provide a rationale to consider heparin monotherapy as the preferred anticoagulant regimen for contemporary PCI.

A Michael Lincoff

Cleveland Clinic Coordinating Center for Clinical Research (C5Research), Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, OH 44195, USA
lincofa@ccf.org

I have received grants from Lilly, AstraZeneca, CSL, Roche, Genentech, Regado, Pfizer, Takeda, and Vivus.

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Dyslipidaemia in perspective

See Series pages 607, 618, and 626

Dyslipidaemia as the original cause of atherosclerotic vascular disease has returned to centre stage, 20 years after the results of the 4S study¹ were published in *The Lancet* in 1994. The 4S study heralded the beginning of the great success of statins, now the most widely prescribed class of drugs in the history of medicine. The three Series papers in this issue of *The Lancet* on the consequences of perturbed lipoprotein metabolism for vascular disease are an education on their own.^{2–4} The authors provide balanced and thorough overviews on what is known and, most importantly, still unknown in the specialty.

LDL cholesterol² has been at the core of atherogenesis for so long in our collective memory that few clinicians have any doubt about its causal role in heart disease. Most clinicians regard familial hypercholesterolaemia to be the best example of that association, and are convinced by the Oxford meta-analysis showing that statins exert their beneficial effects through lowering of LDL cholesterol concentrations.^{5,6} The massive power of the large lipid genetics consortia and their mendelian randomisation approach in dyslipidaemia have further

cemented the role of LDL cholesterol as a cause of atherosclerotic vascular disease.⁷

Nevertheless, not every question has been fully answered, including why has it not been shown convincingly with any other class of drugs that reduction of cardiovascular events follows LDL cholesterol lowering as closely as it does with statins. Despite cholestyramine and partial ileal bypass surgery showing reductions in cardiovascular events in the pre-statin era, results of outcome trials are awaited with a cholesterol absorption inhibitor (IMPROVE-IT [NCT00202878]) and a monoclonal antibody targeting PCSK9 (ODYSSEY Outcomes [NCT01663402], FOURIER [NCT01764633], SPIRE I [NCT01975376], and SPIRE II [NCT01975389]), with success defined as results close to the CTT regression line (ie, a relation that would show an association between LDL cholesterol lowering and event reduction). Such findings should convince sceptics and would make investigation of where the association ends possible; this point is unlikely to be at zero, but will probably be well below 25 mg/dL (0.65 mmol/L), the true physiological LDL cholesterol concentration.

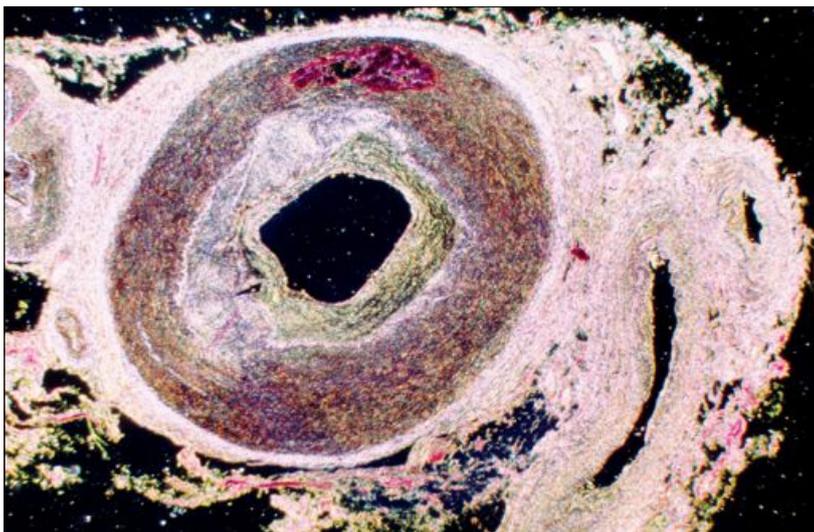
The precise role of inflammation in this LDL-endothelium association is also not completely understood. Patients with the lowest achieved high-sensitivity C-reactive protein concentrations in the JUPITER trial had the lowest event rates, and that finding underscores the importance of inflammatory pathways. However, several candidate anti-inflammatory compounds have recently failed in phase 3 outcome studies after showing encouraging results in phase 2 trials.^{8,9}

Notably, LDL is no longer the only treatment target; meta-epidemiology, loss-of-function mutations, mendelian randomisation, and international collaborations together suggest that triglyceride-rich lipoproteins, remnant cholesterol, and lipoprotein(a) contribute to atherogenesis.³ Establishment of causality, however, needs all of Koch's postulates to be fulfilled and lowering of the concentrations of these particles, with fibrates and nicotinic acid, has either proven futile or harmful.^{10,11} But the very recent and elegant work that unravelled the importance of apolipoprotein C-III in triglyceride metabolism has contributed to a very precise therapy to lower it, an antisense inhibitor that lowered triglyceride concentrations in phase 2 studies.¹²⁻¹⁴ Fish oils are also under investigation in rigorous and well powered randomised controlled trials (REDUCE-IT [NCT01492361] and STRENGTH [NCT02104817]), so perhaps these research questions will be answered soon.

Lowering of lipoprotein(a) has now also come within our reach: PCSK9 monoclonals, cholesteryl ester transfer protein (CETP) inhibitors, and the antisense apolipoprotein(a) inhibitor reduce concentrations of this harmful lipoprotein and intervention studies are eagerly awaited.

However, answers are very far away for HDL.⁴ Epidemiological evidence is strong, but genetics, mendelian randomisation, and results of recent clinical trials question the perhaps too simple concept that increased HDL cholesterol concentrations translate into clinical benefit.

Fortunately, all three lipoproteins (LDL, HDL and triglycerides) share the fact that new therapies to address them are under investigation in outcome trials: ezetimibe and PCSK9 monoclonals for LDL cholesterol (IMPROVE-IT, ODYSSEY Outcomes, FOURIER, SPIRE I, and SPIRE II), fish oils for triglyceride-rich lipoproteins (REDUCE-IT and STRENGTH), infusible HDL mimetics



Artery partially obstructed by atheroma

for HDL cholesterol (AEGIS-1 [NCT02108262]), and CETP inhibitors (REVEAL [NCT01252953] and ACCELERATE [NCT01687998]) for LDL, HDL, and lipoprotein(a).

Ongoing phase 3 programmes will provide answers in the next 5 years to the most important questions in the specialty. Will LDL cholesterol reduction by modalities other than statins yield similar outcome benefits? Will lowering of triglyceride-rich lipoproteins and remnant cholesterol result in a reduction of major adverse cardiovascular events? And, finally, will infusion of pre- β -like HDL particles to promote reverse cholesterol transport from macrophage to circulation lead to an improvement in coronary artery disease risk? After a wait of 20 years, we will have to hold our breath a little longer.

John J P Kastelein

Department of Vascular Medicine, Academic Medical Center/
University of Amsterdam, 1105 AZ, Amsterdam, Netherlands
j.j.kastelein@amc.uva.nl

I am a consultant to and receive honoraria from Dezima Pharmaceuticals, Merck, Cerenis, The Medicines Company, CSL Behring, Amgen, Sanofi, Regeneron, Eli Lilly, Genzyme, Isis, Aegerion, Esperion, AstraZeneca, Omthera, Pronova, Vascular Biogenics, Boehringer Ingelheim, Catabasis, Atheronova, UniQure, Novartis.

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