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Braunwald's Corner

Cholesterol: the race to the bottom

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In 1955, I began my third cardiology fellowship (I was a slow learner) in the Cardiovascular Physiology Laboratory directed by the noted physiologist Stanley J. Sarnoff, in the National Heart Institute (now the NHLBI). One of the other major laboratories in the institute at the time, located on the same floor of the building in which I worked, was focused on lipid biochemistry and the possible relations between dyslipidaemias and coronary artery disease. The senior scientist of the group was Christian B. Anfinsen, a noted biochemist, who was on his way to win a Nobel Prize in Chemistry. When I left the institute in 1968, I had been thoroughly indoctrinated into the lipid hypothesis of atherogenesis and I was convinced of its validity, even though it was not yet accepted by most clinicians, including cardiologists.[1] Our group carried out only a single study in the field, in which we demonstrated in patients with severe hypertriglyceridaemia and peripheral arterial disease that correction of the dyslipidaemia improved blood flow in the legs,[2] suggesting that reduction of hyperlipidaemia might be beneficial in patients with atherosclerotic cardiovascular disease (ASCVD). Although my major research efforts at the time focused on reduction of myocardial infarct size, this clinical study whetted my appetite to look further into potential treatments of dyslipidaemias and I waited for the right opportunity to do so. It was a long wait.

Gradually the clinical evidence for the critical role of cholesterol and of the benefits of cholesterol lowering became accepted. In the USA, the beneficial results of reduction in the Lipid Research Clinics Coronary Primary Prevention trial in 1984 attracted attention.[3] This was followed by a formal consensus conference entitled 'Lowering blood cholesterol to prevent coronary artery disease',[4] and by the report of the European Atherosclerosis Society Study Group on this subject.[5]

I became energized about the clinical management of atherosclerosis when, in 1976, Akira Endo, a Japanese pharmacologist, described, in a three page paper in an obscure journal, the first HMGCoA reductase inhibitor which markedly reduced cholesterol.[6] This was truly a breakthrough (a term I use rarely). The first large, placebo-controlled secondary prevention statin trial was the 4S trial conducted in patients with ASCVD and markedly elevated low-density lipoprotein cholesterol (LDL-C) (avg 4.9 mmol/L).[7] When I learned about the details of the trial, I was convinced that it would be positive, but because the baseline LDL-C levels were much higher than was seen in a large fraction of patients with ASCVD in the USA and other industrialized countries, it would not be directly applicable to them. As expected, 4S was a resounding success. The LDL-C fell by 35% to 3.2 mmol/L, major adverse coronary events (MACE) declined by 34% (*Figure 1*), and total mortality by 30%. Quite appropriately, 4S became a 'landmark' trial overnight.

Shortly after enrolment of patients into 4S was begun, my colleagues Frank Sacks, Marc Pfeffer, and I convinced the Squibb (now the Bristol-Myers Squibb) Corporation to test their new statin, pravastatin, against placebo in patients who had experienced a myocardial infarction, whose conditions were stable and whose LDL-C was similar to the national average for patients with coronary artery disease at the time. The CARE trial began in 1989, 5 years before the 4S trial was reported. At randomization, patients in CARE had an average LDL-C of 3.6 mmol/L. Pravastatin reduced it by 30% to 2.5 mmol/L; MACE, the primary endpoint, was significantly reduced.[8]

It was apparent from 4S and CARE that lowering LDL-C was certainly beneficial for secondary prevention of ASCVD. However, we wondered whether greater lowering would be more effective. We therefore compared pravastatin with the more powerful atorvastatin in the PROVE-IT-TIMI 22 trial, led by Christopher P. Cannon. We enrolled a high-risk post-acute coronary syndrome population and compared pravastatin 40 mg/day, the dose used in CARE, with atorvastatin 80 mg/day, the highest approved dose. The LDL-C was 2.7 mmol/L at baseline and fell to 1.6 mmol/L on atorvastatin. This intensive reduction of LDL-C was significantly more effective in reducing MACE than the moderate effects of pravastatin,[9] with the greater clinical benefit apparent by 2 weeks.

When I presented the results of PROVE-IT to a group of lipidologists, I was asked whether the marked reduction of LDL-C that we produced with atorvastatin was safe. I was quite surprised by the question because the mindset for decades had been to *lower* LDL-C. I was quickly reminded that cholesterol is a critical component of cell membranes and a variety of biochemical reactions including the biosynthesis of several hormones and vitamins. In PROVE-IT, there were 193 patients, 10.5% of those in the atorvastatin arm, who achieved LDL-C levels of <1.04 mmol/L, a level far below the guideline-directed target at the time of 1.8 mmol/L. The analyses of these patients by Stephen D. Wiviott showed that these levels were not associated with any adverse effects but appeared to be associated with a trend to greater efficacy.[10] We breathed a sigh of relief.

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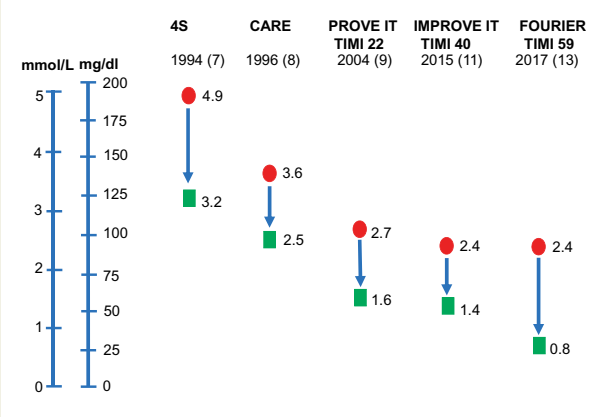

Figure 1 Low-density lipoprotein cholesterol levels at baseline ● and on treatment ■. The dates refer to the first paper providing results and in parentheses their references in this article.

Encouraged by the results of PROVE-IT, we wondered whether even lower LDL-C levels were safe and even more effective. The IMPROVE-IT-TIMI 40 trial, also led by Christopher Cannon, showed that the addition of ezetimibe, a blocker of cholesterol absorption, to simvastatin reduced LDL-C further and improved clinical outcomes, particularly in high-risk patients.[11] In this trial, 971 patients had LDL-C < 0.78 mmol/L, even lower than in PROVE-IT; our colleague Robert P. Giugliano reported that these levels were well tolerated without detectable adverse effects and, when adjusted for baseline variables, exhibited enhanced efficacy.[12]

In the FOURIER-TIMI 59 trial on patients with chronic ASCVD led by Marc S. Sabatine, patients received a statin and the addition of placebo or a PCSK9 inhibitor evolocumab, which lowered LDL-C to an average of 0.78 mmol/L and reduced MACE significantly.[13] Giugliano *et al.* reported that 2669 patients, 20.5% of those in the evolocumab arm, achieved an LDL-C < 0.50 mmol/L; this subgroup had a median level of 0.36 mmol/L with an IQR of 0.28–0.44 mmol/L. Once again, no safety concerns were observed even in patients with 'ultra-low' levels of LDL-C (≤0.28 mmol/L).[14] Thus, it appears that the 'bottom' had been pretty well reached. It was reassuring that the trial which studied alirocumab, a different PCSK9 inhibitor, added to a statin in patients post-acute coronary syndrome also showed that the marked reductions in LDL-C were not associated with any apparent adverse effects.[15]

Comment

It is interesting to compare the LDL-C concentration of 3.2 mmol/L in the active treatment arm of the 4S trial with that of 0.78 mmol/L in the active treatment arm of FOURIER-TIMI 59,[3] a 75% reduction over 23 years, accompanied by a substantial clinical benefit. Although there have been recurrent questions about the safety of these very low levels of LDL-C, there should have been little surprise that they have proved to be safe. Living hunter/gatherer populations have total cholesterol levels between 100 and 130 mg/dL and appear to develop very little atherosclerosis, while newborn infants normally have similar levels at a time of rapid brain development.[16] Also, a number of rare genetic conditions are characterized by ultra-low LDL-C without apparent adverse effect.[17]

For me, this race to the bottom has been an exhilarating experience. While there certainly are additional opportunities for attacking remaining dyslipidaemias, I am cognizant of the enormous strides that have occurred in this field since 1955 when I was first exposed to investigators in an adjacent laboratory who pursued the possible connection between dyslipidaemia and ASCVD.

Conclusions

(1) There is substantial evidence that low levels of LDL-C (<0.5 mmol/L) and even ultra-low levels (<0.3 mmol/L) are well tolerated and safe.
(2) In secondary prevention trials, these low levels might be more effective in reducing MACE than the common guideline target levels of 1.8 and 1.4 mmol/L for high-risk and very high-risk patients, respectively.[18]
(3) It would be desirable and safe to conduct a prospective randomized trial to compare clinical effectiveness at three target levels: 1.4, 0.9, and 0.4 mmol/L.

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Weekly Journal Scan

The EMPEROR-Preserved study: end of the search for the "Phoenix" or beginning of a new season for trials in heart failure with preserved ejection fraction

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Comment on 'Empagliflozin in heart failure with a preserved ejection fraction' published in the *New England Journal of Medicine* (DOI: 10.1056/NEJMoa2107038).

Key Points

- The EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction)[1] (HFpEF) was an industry-sponsored and -funded, double-blind, randomized controlled trial (RCT), carried out to evaluate the efficacy of empagliflozin, a sodium-glucose transporter 2 inhibitor (SGLT2i) in patients with HFpEF.
- A total of 5988 patients (49% with diabetes) with NYHA class II–IV HF and a left ventricular ejection fraction (LVEF) of >40% were randomized to receive empagliflozin 10 mg ($n = 2997$) or placebo ($n = 2991$) in addition to usual therapy. The primary outcome was a composite of adjudicated cardiovascular (CV) death or hospitalization for HF. The first secondary outcome was the occurrence of all adjudicated hospitalizations for HF, including first and recurrent events. The second secondary outcome was the rate of decline in the estimated glomerular filtration rate (eGFR). The median duration of follow-up was 26.2 months.
- A primary composite outcome event occurred in 415 patients (13.8%) in the empagliflozin group and in 511 patients (17.1%) in the placebo group [6.9 vs. 8.7 events per 100 patient-years; hazard ratio (HR), 0.79; 95% confidence interval (CI), 0.69-0.90; $P < 0.001$]. Hospitalization for HF occurred in 259 patients (8.6%) in the empagliflozin group and in 352 patients (11.8%) in the placebo group (HR, 0.71; 95% CI, 0.60–0.83). Death from CV causes occurred in 219 patients (7.3%) in the empagliflozin group and in 244 patients (8.2%) in the placebo group (HR, 0.91; 95% CI, 0.76–1.09). The effects were consistent across prespecified subgroups, including the presence or absence of diabetes at baseline. Empagliflozin reduced the decline in the eGFR compared to placebo (−1.25 vs −2.62 mL/min/1.73 m^2 per year; $P < 0.001$).
- Uncomplicated genital and urinary tract infections and hypotension were more common in patients treated with empagliflozin. Discontinuation of therapy occurred in about 23% of patients in both groups.

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