PROVE-IT proved it: Lower is better – Pro

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Data from prospective epidemiological studies and randomized controlled trials have clearly demonstrated that lower low density lipoprotein cholesterol (LDL-C) concentrations are associated with the greatest reduction in cardiovascular events. Coronary artery disease mortality is lowest in epidemiological studies in those individuals with the lowest cholesterol concentrations. In angiographic studies, patients who had their cholesterol lowered had less angiographic worsening of their atherosclerosis, with those trials that had the lowest on-treatment LDL-C, and especially those that had the greatest percentage of LDL-C lowering, showed the least progression of atherosclerosis. Clinical trials have also highlighted the fact that lower LDL-C concentrations are associated with reduced risk for both a first and a subsequent coronary event with analyses showing that event rates in both primary and secondary prevention trials are directly proportional to on-treatment LDL-C concentrations. An aggressive approach to LDL-C lowering, especially in the high-risk patient, seems warranted.

Key Words: Atherosclerosis; Cholesterol; Coronary disease; Hypercholesterolemia; Lipids; Prevention

Data from both prospective epidemiological studies and randomized controlled trials have clearly demonstrated that lower low density lipoprotein cholesterol (LDL-C) concentrations are associated with the greatest reduction in cardiovascular (CV) events. The present article will review the increasing amount of evidence that supports this view, with an emphasis on the most recent data.

With regard to epidemiological studies, follow up of over 350,000 screeners from the Multiple Risk Factor Intervention Trial (MRFIT) (1) showed that the relationship between serum cholesterol concentrations and the risk of future coronary events is curvilinear, and that the lower the cholesterol, the smaller the risk. Similarly, in the Seven Countries Study (2), coronary artery disease (CAD) mortality was lowest in those individuals with the lowest cholesterol concentrations. Even in a Chinese population with a 'low' average cholesterol of only 4.2 mmol/L, there was a strongly positive relationship between serum cholesterol concentration and death from CAD with no evidence of a threshold (3).

There also exist multiple clinical trials that are consistent with the 'lower is better' hypothesis. In the late 1980s and early 1990s, a large number of so-called angiographic trials were performed in which patients with a clinical history of CAD were randomly

PROVE-IT l'a démontré : Moins c'est mieux

Les données d'études épidémiologiques prospectives et d'essais aléatoires et contrôlés démontrent clairement que de plus faibles concentrations de cholestérol à lipoprotéines de basse densité (LDL) s'associent aux plus fortes diminutions d'événements cardiovasculaires. Dans les études épidémiologiques, le taux de mortalité secondaire à des coronaropathies est le plus faible chez les individus dont les concentrations de cholestérol sont les plus basses. Dans le cadre d'angiographies, les patients qui avaient abaissé leur taux de cholestérol présentaient une aggravation moins marquée de leur athérosclérose dans le cadre des essais où le cholestérol LDL était le plus bas pendant le traitement et, surtout, les essais qui révélaient le plus fort pourcentage de diminution du cholestérol LDL démontraient la plus lente progression d'athérosclérose. Les essais cliniques soulignent également que les concentrations de cholestérol LDL les plus faibles s'associent à une diminution du risque de premier événement coronaire ou d'événement coronaire subséquent, les analyses démontrant que les taux d'événements dans le cadre d'essais sur la prévention primaire et secondaire sont directement proportionnels aux concentrations de cholestérol LDL pendant le traitement. Une démarche énergique pour abaisser le cholestérol LDL semble s'imposer, surtout chez le patient très vulnérable.

assigned to a cholesterol-lowering treatment or no treatment (4). The patients who had their cholesterol lowered had less angiographic worsening of their atherosclerosis and often showed regression of preexisting coronary lesions. It is important to note that although the cholesterol lowering was often achieved with the use of statins, this was not always the case. Cholesterol lowering achieved through lifestyle changes and nonstatin lipid-lowering drugs was also associated with a benefit, highlighting the fact that the observed improvement was not solely a statin effect. A subsequent analysis (5) revealed that those trials that had the lowest on-treatment LDL-C, and especially those that had the greatest percentage LDL-C lowering, showed the least progression of atherosclerosis.

The large statin trials published in the mid 1990s, including the West Of Scotland COronary Prevention Study (WOSCOPS) (6) and Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) (7) in individuals without known CAD, and the Scandinavian Simvastatin Survival Study (4S) (8), Cholesterol And Recurrent Events (CARE) study (9) and the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) study (10) trials in patients with a history of CAD, clearly established that lipid lowering with statins reduced CV events.

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The results left open, however, the questions as to how low the target should be for LDL-C, and whether the LDL-C concentration in patients with coronary disease should be reduced regardless of the baseline concentration. In the WOSCOPS, middle-aged men with high cholesterol concentrations and multiple risk factors had a significant reduction in total and CV events when treated with pravastatin (40 mg/day over five years) than those who took a placebo. A subsequent post hoc analysis suggested a possible threshold because there was no further reduction in risk when LDL-C was reduced beyond 24% (11). The AFCAPS/TexCAPS included men and women with 'average' LDL-C but with low high density lipoprotein cholesterol concentrations, and demonstrated decreased coronary events associated with treatment with lovastatin 20 mg to 40 mg daily over five years.

In the 4S study, conducted in individuals with a history of myocardial infarction (MI) and high cholesterol concentrations, treatment with simvastatin 20 mg to 40 mg daily reduced total mortality by 30% and CV mortality by 42%. A subsequent analysis revealed that patients in the lowest third of on-treatment LDL-C concentrations had the greatest reduction in events, although the relationship between the LDL-C reduction and event reduction did appear to be curvilinear (12). The CARE study, performed in survivors of MI with total cholesterol concentrations less than 6.2 mmol/L randomly assigned to pravastatin 40 mg per day or a placebo, also revealed a significant reduction in coronary events. A post hoc analysis of the study suggested that patients with LDL-C concentrations at baseline of less than 3.2 mmol/L did not show any event reduction associated with further LDL-C reduction. This apparent threshold has not been observed in any other statin study, including LIPID, which used the same drug and dose in a similar study population. LIPID included more than 9000 men and women with a history of CAD between 30 and 75 years of age with total cholesterol concentrations between 4.0 mmol/L and 7.0 mmol/L. Treatment with pravastatin 40 mg daily was associated with a 24% decrease in CV mortality and a 23% decrease in total mortality. Interestingly, baseline cholesterol concentrations analyzed as a continuous variable against event reduction had no impact with even those with the lowest cholesterol concentrations still deriving clinical benefit.

Until recently, the only randomized controlled trial completed to date that attempted to directly answer the question of how low LDL-C should be reduced, is the Post-Coronary Artery Bypass Graft (Post-CABG) trial (13). In this study of 1351 patients with a history of CABG surgery, aggressive LDL-C lowering, including the use of lovastatin, which brought the LDL-C down to an average of approximately 2.5 mmol/L, was associated with an improvement in the primary end point of angiographic progression compared with moderate LDL-C reduction down to a mean LDL-C of approximately 3.5 mmol/L.

The Heart Protection Study (HPS) (14), published in 2002, remains the largest completed statin trial. In this study of 20,536 patients at high risk for CV disease (prior history of CAD, cerebrovascular disease, peripheral artery disease or diabetes) and with a mean LDL-C of 3.4 mmol/L, treatment with simvastatin 40 mg daily was associated with a 24% risk reduction for total CAD, stroke and revascularization. In an a priori analysis, those patients with a baseline LDL-C less than 3.0 mmol/L showed similar event reductions to those with a higher LDL-C.

Furthermore, a post hoc analysis revealed that even among the 3421 patients with a baseline LDL-C less than 2.6 mmol/L, the statin treatment was safe and similarly efficacious as in those with higher baseline LDL-C concentrations.

More recently, two primary prevention studies, both of which compared atorvastatin 10 mg daily with placebo and were terminated prematurely because of overwhelming benefit, were published. In the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) (15), treatment with atorvastatin 10 mg daily was associated with a 36% reduced risk for the primary end point of nonfatal and fatal MI over a median follow-up of 3.3 years in over 19,000 patients with a history of hypertension and at least three other CV risk factors, and a mean LDL-C of 3.4 mmol/L. In the Collaborative Atorvastatin Diabetes Study (CARDS) (16), 2838 patients with type II diabetes and a mean LDL-C of 3.0 mmol/L were randomly assigned to atorvastatin 10 mg daily or placebo. Over a mean follow-up of 3.9 years, the patients assigned to atorvastatin had a 36% reduced risk for acute CAD events and a 48% reduced risk for stroke. It should be noted that the mean on-treatment study LDL-C concentrations for ASCOT and CARDS of 2.2 mmol/L and 2.1 mmol/L, respectively, were both well below currently recommended targets.

In contrast to virtually all of the studies reviewed above, which compared a lipid-lowering drug, most frequently a statin, with a placebo, there have been a number of studies more recently comparing the responses with different statins in different doses, and the results of these studies provide important insights into the 'lower is better' question. In the effects of Atorvastatin and Simvastatin on Atherosclerosis Progression (ASAP) trial (17), 325 patients with familial hypercholesterolemia were treated with either atorvastatin 80 mg or simvastatin 40 mg daily with the primary end point being change in carotid intima media thickness (IMT) over two years. Whereas treatment with atorvastatin was associated with a decrease in IMT of -0.031 mm (95% CI -0.007 mm to -0.055 mm), in the simvastatin group IMT increased by 0.036 mm (95% CI 0.014 mm to 0.058 mm) with the change in thickness between the two groups being significantly different ($P=0.0001$). It should be noted that the percentage decrease in LDL-C was 51% in the atorvastatin-treated patients and 41% in the simvastatin-treated patients.

The next three studies all involved comparisons between atorvastatin 80 mg and pravastatin 40 mg daily. In the Arterial Biology for the Investigation of the Treatment Effects of Reducing cholesterol (ARBITER) study (18), the patients treated with the high-dose atorvastatin had their LDL-C reduced to a mean of 2.0 mmol/L in just over 12 months and showed a decrease $\pm$ SD in carotid IMT of -0.034 ± 0.021 mm, while carotid IMT was stable in the pravastatin group (mean $\pm$ SD change of 0.025 ± 0.017 mm; $P=0.03$), which had a mean LDL-C of 2.8 mmol/L. The Reversal of Atherosclerosis with Aggressive Lipid lowering (REVERSAL) trial (19) used intravascular ultrasound to assess progression of atherosclerosis in 502 patients followed for 18 months. LDL-C concentrations were decreased from a mean of 3.9 mmol/L to 2.9 mmol/L in the pravastatin group, and decreased to 2.1 mmol/L in the atorvastatin group ($P<0.001$). The more intensive LDL-C lowering with the atorvastatin treatment was associated with a significantly lower progression rate in the primary end point of percentage change in atheroma volume relative to the pravastatin therapy ($P=0.02$). In fact, while progression of coronary

Figure 1) Coronary artery disease (CAD) event rates in primary prevention trials (four to five years in duration) are directly proportional to the on-treatment low density lipoprotein (LDL) cholesterol concentrations. The event rate is predicted to approach zero at an LDL concentration of approximately 57 mg/dL (1.5 mmol/L). AFCAPS Air Force Coronary Atherosclerosis Prevention Study; ASCOT Anglo-Scandinavian Cardiac Outcome Trial; P Placebo; S Statin; WOSCOPS West Of Scotland COronary Prevention Study. Adapted from reference 25

atherosclerosis compared with baseline occurred in the pravastatin-treated patients (2.7%; 95% CI 0.2% to 4.7%; $P=0.001$), progression did not occur in the atorvastatin-treated patients (−0.4%; 95% CI −2.4% to 1.5%; $P=0.98$). In an analysis across both treatment groups, it was observed that a 50% LDL-C reduction was required to halt the progression of atherosclerosis.

The PRavastatin Or atorVastatin Evaluation and Infection Therapy (PROVE-IT) trial (20) has provided considerable information on the benefits and safety of marked LDL-C reduction. In 4162 patients with a median LDL-C of 2.7 mmol/L, randomly assigned intensive treatment with atorvastatin within 10 days of an acute coronary syndrome, which brought the LDL-C down to 1.6 mmol/L, was associated with a 16% reduced risk for the primary end point of death or major CV events relative to treatment with pravastatin, which brought the LDL-C down to 2.5 mmol/L over a mean 24 month follow-up. Furthermore, in a post hoc analysis of the results presented at the November 2004 American Heart Association meeting (21), it was demonstrated that those patients on atorvastatin therapy who achieved the lowest LDL-C concentrations had the greatest benefit with no increased safety concerns. Using four-month LDL-C values, the 1756 atorvastatin-treated patients who reached the guideline LDL-C goal of less than 2.6 mmol/L were classified into five groups with the following distribution: greater than 2.6 mmol/L (9%); greater than 2.1 mmol/L to 2.6 mmol/L (reference group, 14%); greater than 1.6 mmol/L to 2.1 mmol/L (31%), greater than 1.0 mmol/L to 1.6 mmol/L (34%) and less than 1.0 mmol/L (34%). Despite having higher risk features at baseline, those with LDL-C less than 1.6 mmol/L and especially those below 1.0 mmol/L had lower event rates than the reference group. Furthermore, despite previously expressed concerns, no differences in total mortality, total stroke or intracranial hemorrhage were observed in the low LDL-C group compared with the reference group. In addition, no significant differences in the occurrence of elevated liver enzymes, discontinuation due to elevated liver enzymes, clinical rhabdomyolysis or elevated creatine kinase enzymes were observed between the low LDL-C groups and the reference group.

Figure 2) Coronary artery disease (CAD) event rates in secondary prevention trials (five years in duration except the PRavastatin Or atorVastatin Evaluation and Infection Therapy [PROVE-IT] Study, which was two years in duration) were directly proportional to on-treatment low density lipoprotein (LDL) cholesterol concentrations. The event rate is predicted to approach zero at LDL of 30 mg/dL (0.8 mmol/L). 4S Scandinavian Simvastatin Survival Study; CARE Cholesterol And Recurrent Events trial; HPS Heart Protection Study; LIPID Long-term Intervention with Pravastatin in Ischemic Disease trial; P Placebo; S Statin. Adapted from reference 25

The recently published Treating to New Targets (TNT) study (22,23) is the first randomized clinical trial to prospectively assess the efficacy and safety of treating patients with stable CAD to LDL-C concentrations significantly below 2.6 mmol/L. A total of 10,001 men and women with stable CAD and an LDL-C below 3.4 mmol/L after eight weeks of an open-label atorvastatin 10 mg daily run in were randomly assigned in a double-blind manner to either atorvastatin 10 mg or 80 mg daily for a median follow-up of 4.9 years. The mean LDL-C concentrations over the entire study period were 2.6 mmol/L for the 10 mg group and 2.0 mmol/L for the 80 mg group. The primary end point (occurrence of a major CV event defined as death from CAD, nonfatal nonprocedure-related MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke) was significantly reduced by 22% ($P=0.002$) (absolute risk reduction of 2.2%) in the patients randomly assigned to atorvastatin 80 mg daily. Although there was no difference in all-cause mortality, it should be noted that the study was not powered to detect differences in this end point and that the mortality rate in both arms of the study was much less than that observed in the previous landmark statin trials, likely reflecting the excellent control of lipids in both groups in the TNT study as well as the greater usage of other evidence-based therapies in this contemporary study. Persistent elevations in liver transaminases were observed in 1.2% of the atorvastatin 80 mg versus 0.2% in the atorvastatin 10 mg treated patients ($P<0.001$).

SUMMARY

It can thus be observed that there are increasing data highlighting the fact that lower LDL-C concentrations are associated with reduced risk for both a first and subsequent coronary event. In fact, analyses of the completed trials have clearly shown that the CAD event rates in both the primary prevention (Figure 1) and secondary prevention (Figure 2) trials are directly proportional to the on-treatment LDL-C concentrations with the lowest event rates occurring in the trial groups with the lowest LDL-C concentrations. Lipid guidelines in Canada (24) and the United States (25) had suggested a target

LDL of less than approximately 2.5 mmol/L to 2.6 mmol/L in high-risk patients with CAD or coronary equivalents. The United States National Cholesterol Education Program had suggested in 2004 that clinicians consider a target LDL-C of 1.8 mmol/L in very high-risk patients, such as those with an acute coronary syndrome or with diabetes plus CAD (26), and other authors have proposed target LDL-C concentrations as low as 1.3 mmol/L to 1.7 mmol/L (27). The findings of the TNT trial suggest that it now appears to be justified to recommend reducing LDL-C to at least below 2.0 mmol/L in patients with CAD or CAD equivalents. Other clinical trials currently underway, such as the Incremental Decrease in End Points through Aggressive Lipid lowering (IDEAL) study (28) and

the Study Evaluating Additional Reduction in Cholesterol and Homocysteine (SEARCH), both of which are comparing more aggressive versus less aggressive LDL-C reduction strategies in high-risk patients, should provide additional data and are expected to report in the near future. In the interim, an aggressive approach to LDL-C lowering, especially in the high-risk patient, certainly seems warranted.

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