PROVE-IT proves that lower is better: A contrary view

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Epidemiological studies have demonstrated that low density lipoprotein (LDL) cholesterol and C-reactive protein (CRP) are both independent risk factors for future cardiovascular events. Statin therapy, initially developed to modify blood lipid concentrations, has also been shown to have potentially important pleiotropic effects, including a reduction in CRP concentrations. Recent clinical trials have demonstrated conflicting results regarding the benefits associated with intensively lowering LDL cholesterol. An analysis of these results suggests that the different effects of specific statins on CRP concentrations may be an important determinant of the observed overall benefit associated with therapy. These studies together prove that while lowering LDL is beneficial, lowering LDL and CRP is better.

Key Words: *Atherosclerosis; CRP; Lipids; Statins*

L'évaluation de la pravastatine ou de l'atorvastatine et la thérapie contre l'infection démontrent que moins, c'est mieux : Un point de vue opposé

Des études épidémiologiques ont démontré que le cholestérol à lipoprotéines de basse densité (LDL) et que la protéine C-réactive (PCR) sont tous deux des facteurs de risque indépendants de futur événement cardiovasculaire. Il est également démontré que la thérapie aux statines, créée pour modifier les concentrations de lipides sanguins, a des effets pléiotropes démontrés qui peuvent être considérables, y compris une réduction des concentrations de PCR. De récents essais cliniques ont révélé des résultats conflictuels quant aux bienfaits d'une diminution intensive du cholestérol LDL. Une analyse de ces résultats laisse supposer que les différents effets de statines précises sur les concentrations de PCR peuvent constituer un déterminant important des bienfaits globaux observés par suite de cette thérapie. Ensemble, ces études indiquent que si la réduction du cholestérol LDL est bénéfique, la diminution conjointe du cholestérol LDL et de la PCR est préférable.

Recent clinical trials have demonstrated that more intensive statin therapy dosing is superior to moderate dosing in the reduction of cardiovascular events. This also holds true for individuals among whom blood lipid concentrations are average or only slightly above average. However, it remains unclear how intensive statin therapy works. Are the observed benefits due entirely to the associated changes in blood lipid concentrations, or do statins modify the atherothrombotic process by multiple pathways? Unfortunately, there are no clinical trial data presently available to conclusively prove that the pleiotropic effects associated with statin therapy provide incremental benefits beyond those associated with lowering low density lipoprotein (LDL) cholesterol. Nonetheless, a number of recently published studies provide evidence that the inconsistent results observed in intensive statin-lowering trials can be explained by factors other than LDL cholesterol.

In the PRavastatin Or atorVastatin Evaluation and Infection Therapy (PROVE-IT) study, 80 mg of atorvastatin reduced LDL cholesterol concentrations significantly more than 40 mg of pravastatin (1). Over 24 months of follow-up, death or major cardiovascular events were also lower among atorvastatin-treated patients. This was the first major clinical trial to demonstrate that intensive statin therapy was superior to moderate therapy in reducing cardiac events. As this study was designed to evaluate the benefits of intensive LDL-lowering, the positive results were ascribed to the 42% reduction in LDL associated with atorvastatin compared with the 10% reduction observed with pravastatin.

Falling on the heels of the PROVE-IT study, the A to Z Trial compared intensive simvastatin therapy with placebo, followed by moderate simvastatin treatment (2). In this particular study, intensive statin therapy was associated with a marked reduction in LDL cholesterol compared with less aggressive therapy. While there were strong trends in favour of intensive therapy, few of the prespecified primary end points were statistically significant. Once again, intensive statin therapy with simvastatin was associated with a marked reduction in LDL cholesterol compared with less aggressive statin therapy. While this negative result may represent a problem with inadequate sample size, it is worth noting that after six months of follow-up, there was still no clear-cut benefit of intensive treatment. On the other hand, in the PROVE-IT study, the benefits of intensive therapy could be identified after only three months of treatment. Both studies were associated with substantial reductions in LDL cholesterol associated with intensive treatment. Why the different results?

One possible explanation is the differential effects on C-reactive protein (CRP) observed in the two studies. In the A to Z study, the differential effect on LDL concentrations among intensively versus moderately treated patients ranged

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from 0.39 mmol/L to 1.61 mmol/L (3). On the other hand, in PROVE-IT study, the LDL differential ranged from 0.73 mmol/L to 0.86 mmol/L between the two treatment arms. In other words, the observed changes in blood lipid concentrations were comparable between the two clinical trials. On the other hand, the incremental effect of intensive statin therapy on CRP concentrations in the PROVE-IT study was an additional 38% reduction compared with only a 17% reduction in the A to Z study. This suggests that intensive statin therapy in one trial may have been associated with a greater anti-inflammatory effect on the vulnerable plaque. In other words, the smaller anti-inflammatory effect in the A to Z study may have been responsible for the smaller reduction in events. The question remains, can one prove that CRP is a risk factor independent of LDL cholesterol, and that reducing CRP concentrations in and of itself reduces the risk of an atherothrombotic event?

There are a number of studies that clearly demonstrate that CRP is an independent risk factor for cardiovascular events. Ridker and colleagues (4) analyzed data from the Women's Health Study (WHS), which clearly showed that the age-adjusted RR of cardiovascular disease was more strongly associated with CRP concentrations than LDL cholesterol concentrations. In a second analysis using data from the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCaps), it was also demonstrated that lovastatin therapy was effective in preventing cardiovascular disease among most patients except one subgroup: those with LDL cholesterol concentrations and CRP concentrations below the median (5). For all other combinations of LDL and CRP, lovastatin therapy appeared to be associated with a reduction in cardiovascular risk. In other words, the only situation in which statin therapy was not beneficial was when both independent risk factors were already at low concentrations.

Finally, a recent clinical trial among patients with rheumatoid arthritis has clearly demonstrated that statin therapy is associated with an anti-inflammatory effect. Specifically, in the Trial of Atorvastatin in Rheumatoid Arthritis (TARA) (6), patients with active rheumatoid arthritis who were already receiving anti-inflammatory, immunosuppressive and antibiological therapy were randomly assigned to receive atorvastatin or placebo treatment to modify the progression of their arthritis. After six months of follow-up, the statin-treated group was observed to have a significant reduction in their global disease activity score, CRP concentrations and number of inflamed joints. Compared with the control group, statin therapy reduced the manifestations of active rheumatoid arthritis. This clearly demonstrates that statins possess anti-inflammatory activity. Unless one believes that LDL cholesterol is an important mediator of inflammation in rheumatoid arthritis, the only other explanation is that the anti-inflammatory effect of statins was mediated through inflammatory factors such as CRP.

There is no study to date that has proven that modifying CRP concentrations without changing LDL cholesterol is associated with a reduction in cardiovascular events. However, the inconsistent results observed in the PROVE-IT and A to Z studies suggest the real possibility that CRP may be an important independent and modifiable risk factor for cardiovascular events. This marker of inflammation has been shown to be independently associated with cardiovascular disease after adjustment for established risk factors. Moreover, the TARA study has demonstrated that statin therapy is associated with a significant anti-inflammatory effect.

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