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A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO, ONTARIO

Scientific Update™

The Aggressive Lipid-Lowering Initiation Abates New Cardiac Events (ALLIANCE) Study

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A Report on a Presentation at the American College of Cardiology 53rd Annual Scientific Sessions

New Orleans, Louisiana March 7-10, 2004

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The statin drugs have become the mainstay of vascular protection for reducing the incidence of the major outcomes of death, heart attack, and stroke. Both the National Cholesterol Education Program – Adult Treatment Panel III (NCEP ATP III)[1] and the Canadian guidelines[2] for lipid control place great emphasis on reducing low-density lipoprotein cholesterol (LDL-C) to target levels that were determined based on evidence from clinical trials. Yet, the optimal level of LDL-C remains controversial. Recent evidence suggests that enhanced benefits may be obtained with greater LDL-C reduction and that similar benefits are observed, whatever the starting level of LDL-C. The Aggressive Lipid-Lowering Initiation Abates New Cardiac Events (ALLIANCE) Study[3] compared an aggressive lipid-lowering strategy with usual medical care to achieve LDL-C levels below NCEP current targets in patients with a history of coronary artery disease (CAD).

Lower LDL cholesterol is better

Epidemiological studies, including the Multiple Risk Factor Intervention Trial (MRFIT),[4] the Framingham Study,[5] and the Prospective Cardiovascular Munster (PROCAM) trial,[6] relate the development of coronary heart disease to cholesterol levels. Lower cholesterol levels – even in ethnic groups with lower than average levels – are associated with lower rates of cardiovascular events. However, it was not until the Scandinavian Simvastatin Survival Study (4S)[7] that a reduction in total cholesterol was clearly shown to reduce cardiovascular mortality in patients with proven CAD. The benefits of lowering LDL-C are seen in patients with and without known CAD, in women, in older patients, in diabetic patients, following myocardial infarction (MI), and in different ethnic populations. Large prospective studies in >100,000 patients have confirmed that the reduction in cardiovascular events is proportional to both the overall reduction in LDL-C and the level of LDL-C achieved during treatment (Figure 1).[7-12] The 4S study[7,13] also demonstrated that the tertile of patients achieving an LDL-C between 1.5 and 2.7 mmol/L had the lowest rates of coronary events (Figure 2). The Heart Protection Study (HPS)[9] revealed that the same reductions in cardiovascular endpoints are achieved in patients with baseline LDL-C levels of <2.6 mmol/L as in those with higher LDL-C levels. Yet, the Cholesterol and Current Events (CARE) study[10] suggested there was no additional benefit in lowering LDL-C to below the baseline value of 3.23 mmol/L. Recent evidence now demonstrates the benefits of both lowering LDL-C to well below current target levels of 2.5 mmol/L, as well as from initiating treatment in high-risk patients, however low their LDL-C.

ALLIANCE

The ALLIANCE study was a 4-year, population-based, open-label, randomized study that compared aggressive lipid-lowering with atorvastatin to usual medical care in a managed healthcare environment.[3] The primary objective was to test the hypothesis that lowering LDL-C to levels lower than current NCEP guidelines would provide an incremental reduction in major cardiovascular events compared to standard clinical practice in patients with CAD.

Men and women, aged 18 to 75 years, with prior CAD were identified from managed healthcare organization databases. Prior CAD was defined as prior MI >3 months before screening, percutaneous coronary intervention (PCI) >6 months before screening, coronary artery bypass graft (CABG) surgery >3 months before screening, or unstable angina >3 months before screening. Stable exertional angina was not an entry criterion. The lipid criteria for the study were LDL-C >3.36, but <6.46 mmol/L for patients *not*

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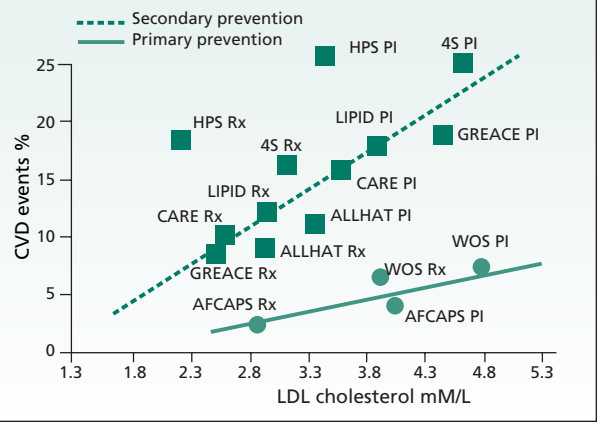
Figure 1: The relationship between the change in cholesterol and reduced cardiovascular outcomes in clinical trials



receiving lipid-lowering medication and LDL-C >2.84, but <5.17 mmol/L for patients receiving lipid-lowering medication.

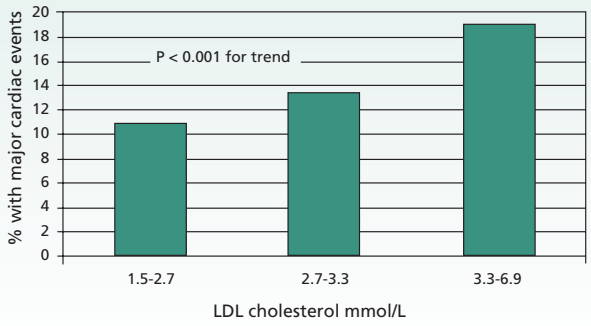
The ALLIANCE study included 2442 patients with CAD who were randomized to receive either atorvastatin 10-80 mg/day, titrated to a dose to reduce LDL-C to < 2.07 mmol/L, or usual care that could include lifestyle modification, diet, and medications provided by their primary care physician. The patients in both arms of the trial were well-matched, with a mean age of 61 years, 82% were male, average weight 88.7 kg, 22% were diabetic, and 58% had a history of prior MI.

Results

The initial LDL-C level was 3.8 mmol/L in both arms of the study. The patients in the atorvastatin group, titrated to a maximum dose of 80 mg daily (mean 40.5 mg/day) achieved a final LDL-C of 2.46 mmol/L, whereas the LDL-C in the usual care group was 2.87 mmol/L. The primary endpoint of the trial was a composite of cardiac death, non-fatal MI, resuscitated cardiac arrest, cardiac revascularization, and unstable angina requiring hospitalization. Over the average 52 months of the trial, the ALLIANCE study showed that treatment with atorvastatin resulted in a 17% reduction in the primary composite endpoint compared with usual care (Figure 3). Of the components of the primary composite endpoint (Figure 4), there was a striking 47% reduction in non-fatal MI (p=0.0002; Figure 5). Furthermore, the benefit from the reduction of non-fatal MI was seen within months of initiating treatment with atorvastatin. In the group managed aggressively with atorvastatin, 72% achieved the ATP III target LDL-C goal of 2.59 mmol/L, compared to only 40% in the usual care group (p<0.0001).

Lipid-lowering therapy was well tolerated in the 2 study arms with a similar frequency of serious adverse side effects in both groups. Atorvastatin treatment was associated with a low incidence of liver transaminase elevation to levels >3 times the upper limit of normal (aspartate aminotransferase [AST] 0.7% and alanine aminotransferase [ALT] 1.3%). No cases of either rhabdomyolysis or myopathy were observed.

Figure 2: Achieved LDL cholesterol (by tertiles) on treatment with simvastatin, related to the incidence of major cardiac events during the 5 years of treatment in the 4S study[13]

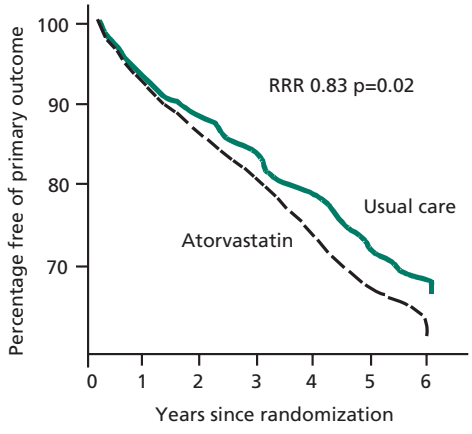


The conclusions of the ALLIANCE study are that aggressive LDL-C lowering with atorvastatin provides an incremental clinical benefit compared to usual care provided in a managed care system. Furthermore, this aggressive management strategy was not associated with any increase in adverse outcomes.

Commentary

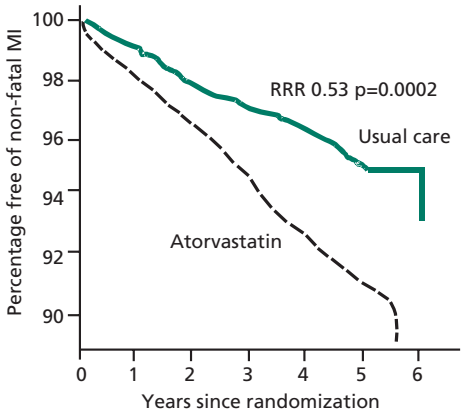
The ALLIANCE trial was undertaken between July 1995 and October 1998 in an era of changing guidelines. During the period of the trial, physicians would have been influenced by NCEP-ATP II, Health Plan Employer Data and Information Set (HEDIS), and ATP III. In contrast, patients randomized to the atorvastatin arm of the study had one management strategy. Thus, the usual care targets were probably not constant throughout the period of the trial. Furthermore, there are few details available about "usual care." It is important to know whether other cardiac risk factors, such as blood pressure

Figure 3: ALLIANCE – The primary composite outcome* in the atorvastatin-treated and usual-care patients



* Cardiac death, non-fatal MI, resuscitated cardiac arrest, cardiac revascularization, and unstable angina requiring hospitalization

Figure 4: ALLIANCE – Reduction of nonfatal MI in the atorvastatin versus the usual care group



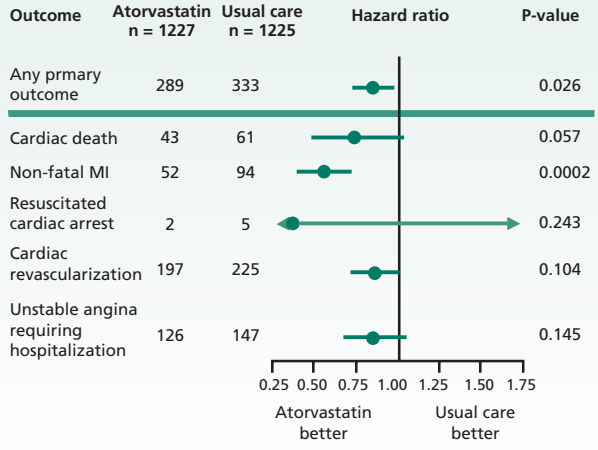
control and smoking cessation, were similarly managed in the 2 arms of the trial.

Since the study was initiated 9 years ago, with many of the patients in the usual care group treated according to old standards, are the results relevant today? Unfortunately, in the real world, lipid-lowering standards have not kept up with guidelines.[14] Thus, the study is highly relevant today and emphasizes the need to aggressively reduce cholesterol using a powerful and effective lipid-lowering agent such as atorvastatin.

Perhaps greater benefits would have been achieved if a larger proportion of patients in the aggressively-treated group had achieved the target LDL-C level of 2.07 mmol/L. This may have been attainable if more patients had been titrated to receive the maximum dose of atorvastatin, (80 mg daily), since the mean dose of atorvastatin in the treatment group was only 40.5 mg/day.

Other studies have confirmed the benefit of more aggressive lipid-lowering. The Post-Coronary Artery Bypass Graft Trial[15] showed a 50% reduction in the progression of atherosclerosis using an aggressive strategy with LDL-C reduction targeted to 2.4 to 2.5 mmol/L versus a more moderate target of 3.4 to 3.6 mmol/L. The recently reported studies, REVERSAL[16] and PROVE-IT,[17] also confirm the hypothesis that aggressive lowering of LDL-C to levels below current targets provides enhanced benefit.

Figure 5: ALLIANCE – Hazard ratios for the primary outcome and individual components for the atorvastatin and usual care groups



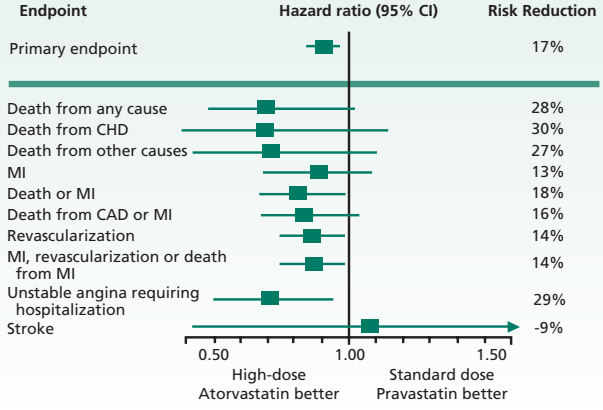
REVERSAL

The Reversing Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial[16] compared the effects of aggressive lipid-lowering with atorvastatin, 80 mg daily (final LDL-C 2.04 mmol/L), to a more moderate treatment with pravastatin, 40 mg daily (final LDL-C 2.8 mmol/L) on CAD progression measured by intracoronary ultrasound in patients with stable CAD. During the 18-month follow-up, atorvastatin 80 mg daily was shown to be superior to pravastatin 40 mg in arresting the progression of coronary atherosclerosis. The atorvastatin-treated patients had no significant progression in atheroma volume; however, the pravastatin group had a 2.7% increase (p=0.02). Although LDL-C was lowered more by atorvastatin, analysis of the results suggests that LDL-C reduction alone does not explain all the differences in efficacy observed between the atorvastatin and pravastatin groups. Patients in the atorvastatin treatment group had a significantly greater reduction in C-reactive protein, but whether this is a consequence of greater LDL-C reduction or a pleiotropic effect of atorvastatin is unknown.

PROVE-IT

The Pravastatin or Atorvastatin Evaluation and Infection Therapy trial (PROVE-IT),[17] compared the effect of pravastatin 40 mg daily (standard therapy) with atorvastatin 80 mg daily (intensive therapy) in 4162 patients, hospitalized in the preceding 10 days with an acute coronary syndrome (ACS). The LDL-C achieved during the 24-month treatment with pravastatin and atorvastatin was 2.46 mmol/L and 1.60 mmol/L, respectively. Atorvastatin was shown to be superior to pravastatin,

Figure 6: PROVE-IT Study – Hazard ratios for the primary endpoint (all-cause mortality, or major cardiovascular event), the components of the primary endpoint, and the secondary endpoints in the atorvastatin versus the pravastatin group[17]



with a 17% reduction in the primary composite endpoint (all-cause death, MI, unstable angina, revascularization, and stroke; Figure 6). Death or MI was reduced by 18%, need for revascularization by 14%, and unstable angina requiring hospitalization by 29%. A reduction in events from the intensive lipid-lowering strategy with atorvastatin was observed as early as 30 days after initiating treatment. Furthermore, atorvastatin 80 mg daily was well tolerated at the higher dose and the discontinuation rates of both agents due to patient preference or adverse side effects were similar.

Neither the PROVE-IT nor REVERSAL trials conclusively show that the additional cholesterol-lowering achieved by atorvastatin 80 mg daily was responsible for the enhanced benefits compared to the effect of treatment with pravastatin 40 mg daily. Pleiotropic benefits of atorvastatin could have provided additional benefits. Only a trial with the two statins that titrated LDL cholesterol levels to similar targets could have attributed differences to pleiotropic effects.

The PROVE-IT study supports the results of the MIRACL study,[18] in which atorvastatin 80 mg daily was compared to placebo. Atorvastatin, started in patients with ACS within 96-hours of presentation and irrespective of baseline LDL-C, reduced the primary endpoint of all-cause mortality, non-fatal MI, resuscitated cardiac arrest, and worsening angina requiring urgent hospitalization, during the 16-week treatment period (RR 0.84, p=0.048). PROVE-IT confirms that administration of atorvastatin 80 mg soon after ACS results in early and greater long-term benefits than can be achieved with pravastatin 40 mg daily.

Conclusions

- The ALLIANCE study shows the incremental benefit of an aggressive strategy of LDL-C-lowering with atorvastatin (mean dose 40.5 mg daily to achieve a final LDL-C of 2.46 mmol/L), compared with usual care in a managed care environment (achieving a final LDL-C of 2.87 mmol/L).
- The aggressive strategy using atorvastatin resulted in a 17% reduction in the primary composite endpoint compared to usual care. MI was reduced by 47% in the atorvastatin patients.
- The REVERSAL and PROVE-IT trials demonstrated the benefits of aggressive LDL-cholesterol lowering with atorvastatin 80 mg compared to a modest LDL-C reduction with pravastatin 40 mg. In REVERSAL, atorvastatin 80 mg daily halted the progression of atherosclerosis and in PROVE-IT, the same dose resulted in an important reduction of adverse cardiovascular outcomes compared to patients receiving pravastatin 40 mg daily.
- In both patients with stable, chronic, CAD and in those with recent acute coronary syndromes, an aggressive LDL-C-lowering strategy that includes atorvastatin, results in improved outcomes.

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Dr Fitchett reports that he has received speaker and consultant fees from Merck Frosst Canada, Sanofi-Synthelabo Canada, Bristol-Myers Squibb Canada, Aventis Pharma Inc, Schering Canada Inc, Biovail Pharmaceuticals, Pfizer Canada Inc, and Hoffmann-La Roche Ltd.

SNELL Medical Communication acknowledges that it has received an unrestricted educational grant from Pfizer Canada Inc. to support the distribution of this issue of *Cardiology Scientific Update*. Acceptance of this grant was conditional upon the sponsors' acceptance of the policy established by the Division of Cardiology and SNELL Medical Communication guaranteeing the educational integrity of the publication. This policy ensures that the author and editor will at all times exercise unrestricted, rigorous, scientific independence free of interference from any other party.