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Scientific Update™

Where Have We Been? Where Are We Going? A Forum on Statin Therapy and Clinical Trials.

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Few areas of medicine can rival the accumulated evidence on the use of statins in the prevention of cardiovascular (CV) disease. Over 100,000 patients have been randomized in large primary and secondary prevention trials using statins in patients with stable coronary heart disease, acute coronary syndromes, and in high risk populations. More recent trials support the use of potent statins in high doses to achieve aggressive reductions in low-density lipoprotein cholesterol (LDL-C) and greater clinical benefit and some clinical guidelines have lowered the recommended targets in high risk patients. However, concern about the safety of high-dose statins may prevent some clinicians from using them at the doses shown to be effective in clinical trials. This issue of *Cardiology Scientific Update* provides a historical review of statin trials with an emphasis on those conducted with the 80 mg dose of atorvastatin since they are predominantly responsible for the new lower targets in the guidelines. New safety and efficacy data derived from those trials are also discussed.

An overview of statin clinical trials

The remarkable story of the statins in North America began – at least from the point of view of clinical practice – with the introduction of lovastatin in 1987. In 1993, the statins were included in the guidelines of the U.S. National Cholesterol Education Program (NCEP). Then, in 1994, there was the publication of the Scandinavian Simvastatin Survival Study (4S),[1] a secondary prevention study and the first landmark study with a statin. It was also the trial that definitively proved the lipid hypothesis. The value of the statins in primary prevention was first established by the West of Scotland Coronary Prevention Study (WOSCOPS), published in 1995.[2] Many other clinical trials confirmed the initial results and conclusively extended the benefits of statin therapy to progressively lower risk groups.

The greatest risk of recurrent events leading to death or nonfatal myocardial infarction (MI) following an acute coronary syndrome (ACS) occurs relatively soon after the initial presentation. An obvious question that was raised was whether statins would work fast enough after an ACS to have an impact on early events. This question was addressed in 2000 by the Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial,[3] and more definitively in 2004 by the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) study.[4] To understand the importance of the initial statin landmark trials, it is necessary to understand the context in which they were conducted, when the "lipid hypothesis" had not yet been proven and many phyisicians remained skeptical. For instance, Heart Failure, a book published in 1989, attacked the "cholesterol myth" and stated that "lowering your cholesterol is next to impossible with diet, often dangerous with drugs, and won't make you live any longer" (T. J. Moore, Random House). This was subsequently refuted by the results of the 4S, which demonstrated a 30% reduction in total mortality with simvastatin in patients with stable coronary heart disease (CHD).[1]

In 1996, the Cholesterol and Recurrent Events (CARE) study was conducted in post-MI patients who had "average" total and LDL-C levels. It demonstrated that pravastatin could reduce fatal coronary heart disease and nonfatal MI by 24%.[5] Subsequently, the Heart Protection Study (HPS), by virtue of its large sample size, was able to show that patients at risk of CHD benefited from treatment with simvastatin, irrespective of their

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baseline LDL-C level. In fact, even patients with LDL-C levels <2.6 mmol/L, which was until recently the recommended target for high-risk patients in the U.S., derived the same benefit as those with much higher baseline levels.[6]

The analysis of the earlier trials also suggested that when LDL-C is lowered more aggressively, the reduction in events is greater, signifying a possible role for more potent statins at higher doses. This led to a new era, when studies were no longer placebo-controlled, but included the comparison of "intensive" versus "moderate" LDL-C reduction. Many of these trials, such as ARBITER (Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol),[7] ASAP (Atherosclerosis Progression in Familial Hypercholesterolemia),[8] and REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering)[9] utilized atorvastatin, a potent agent that was introduced in 1997. Both ARBITER and ASAP studied the surrogate endpoint of carotid artery intimal-medial thickness and demonstrated the superiority of atorvastatin over pravastatin and simvastatin, respectively, in causing regression of carotid atherosclerosis.

More recent studies have been conducted using coronary intravascular ultrasound. REVERSAL showed the superiority of intensive LDL-C lowering with atorvastatin in arresting the progression of coronary atherosclerosis. Although it did not compare aggressive versus moderate LDL-C reduction, one recent study also warrants discussion because it reinforces the conclusion that aggressive LDL-C lowering is associated with highly beneficial effects on coronary atherosclerosis. The Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID) demonstrated that aggressive LDL-C lowering could cause regression of coronary atherosclesrosis.[10]

In addition to the trials that evaluated surrogate endpoints, trials that assessed clinical outcomes also compared strategies of intensive versus moderate cholesterol reduction. Trials in patients with an ACS included PROVE-IT,[4] which compared atorvastatin 80 mg with pravastatin 40 mg, and the Aggrastat to Zocor (A to Z) trial, which compared high- and low-dose simvastatin.[11] Two large trials were also conducted in patients with stable CHD: the Treating to New Targets (TNT) study compared atorvastatin 80 mg with 10 mg of the same statin,[12] and IDEAL compared high-dose atorvastatin (80 mg) with simvastatin 20 and 40 mg.[13] In the regression trials of intensive cholesterol lowering with atorvastatin 80 mg, the LDL-C levels achieved were 1.95 mmol/L in ARBITER[7] and 2.05 mmol/L in REVERSAL.[9] In the outcome trial, PROVE-IT, the LDL-C level achieved was 1.6 mmol/L with atorvastatin 80 mg and 2.46 mmol/L with pravastatin 40 mg.[4] This was associated with a 19% relative risk reduction. Similarly, the intensive reduction arm in TNT, utilizing atorvastatin 80 mg, resulted in an LDL-C level of 2.0 mmol/L and a reduction in the risk of 22% compared to a moderate reduction with atorvastatin 10 mg, which reduced LDL-C to 2.6 mmol/L on average.

The challenge that faced the primary prevention trials was somewhat different. Safety and cost-effectiveness played a more prominent role and there was a greater emphasis on the identification and treatment of high-risk cohorts. Consequently, WOSCOPS enrolled patients with high LDL-C,[2] AFCAPS/TexCAPS included patients with low high-density lipoprotein cholesterol (HDL-C),[14] ASCOT-LLA recruited patients with multiple risk factors,[15] and the Atorvastatin Diabetes Study (CARDS) included patients with type 2 diabetes mellitus, but without symptoms or history of prior CHD.[16] One way to assess cost-effectiveness is to calculate the numbers needed to treat (NNT), which were 12 and 34 in 4S and CARE, respectively.[1,5] The NNTs were obviously higher in the primary prevention studies, although not markedly, reaching 46 in WOSCOPS,[2] 50 in AFCAPS,[14] and 60 in ASCOT.[15] Remarkably, in CARDS,[16] which enrolled only type 2 diabetic patients without CHD, the NNT was 27, well in the range of the secondary prevention trials.

Reducing stroke risk with statin therapy

Mortality rate after a stroke is high and reaches 40%-60% at 5 years. The recurrence after a stroke is also high as 25%-40% of the patients have recurrent events at 5 years.[17] Other devastating consequences are total or partial dependency that can reach 50% and dementia that can affect up to 34% of the patients. Moreover, a meta-analysis in >90,000 patients enrolled in statin trials revealed a 21% all-stroke risk reduction with statins.[18] Additionally, there was a strong correlation between the degree of cholesterol reduction achieved with the statin and risk reduction. For each 10% reduction in LDL-C, the relative risk of stroke was decreased by 13.2%. ASCOT also reported important results with respect to stroke. Compared to placebo, the relative risk of fatal and nonfatal stroke was reduced by 27% with atorvastatin 10 mg.[15]

Anti-hypertensive therapy lowers the risk of stroke by 36%-40%. What is most remarkable about ASCOT is that all of the patients were actively treated with anti-hypertensive agents, and, therefore, the 27% risk reduction seen with atorvastatin occurred in addition to the benefits of lowering blood pressure. The results of the stroke outcomes in the CARDS trial are also remarkable. This study enrolled relatively healthy type 2 diabetic patients with no prior CHD and a mean LDL-C of 4.14 mmol/L or lower. The trial was terminated 2 years earlier than expected since the pre-specified efficacy criteria had been met. Compared to placebo, the risk of stroke was reduced by 48% with atorvastatin 10 mg.[16]

The SPARCL trial

The largest study of statin treatment in stroke patients is the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial.[19] It enrolled 4,731 patients who had suffered a stroke or transient ischemic attack (TIA) within the previous 6 months, had no history of CHD, and had LDL-C levels between 2.6 and 4.9 mmol/L. Patients were randomized to atorvastatin 80 mg daily or placebo. The mean baseline LDL-C was 3.4 mmol/L, while the mean on-treatment concentrations were 3.3 mmol/L in patients randomized to placebo and 1.9 mmol/L in patients randomized to high-dose atorvastatin. The pre-specified primary endpoint of fatal and nonfatal stroke was significantly reduced by 16%. Importantly, the risk of fatal stroke was reduced by 43%. The patients enrolled in SPARCL had no known history of CHD and treatment with atorvastatin 80 mg

resulted in a 35% reduction in the risk of major coronary events and a 45% reduction in the risk of any revascularization. SPARCL is the only study to demonstrate that in patients with a recent stroke or TIA, treatment with a statin not only reduces recurrent cerebrovascular events, but also coronary events and revascularizations.[19] Treatment with atorvastatin 80 mg in SPARCL was accompanied by acceptable safety and tolerability. Almost all of the patients in the study were statin-naïve, there was no run-in period and there was no titration of the dose of the statin, since only atorvastatin 80 mg was used in the active treatment arm. The incidence of an elevation in ALT or AST was only 2.2%. Total CPK ≥10 times upper limit of normal was only 0.1%. Of note, there was no difference in the incidence of myalgia, myopathy, or rhabdomyolysis between atorvastatin 80 mg and placebo.

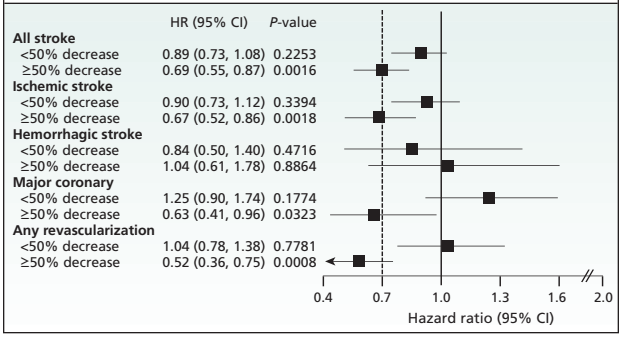
At the time that SPARCL was being conducted, evidence was accumulating that suggested the benefits of statins in the prevention of stroke in populations at high-risk, but there was no evidence that this was the case in patients with prior cerebrovascular disease. This led to 22% of the patients randomized to placebo being prescribed open label statins by their physicians. Consequently, the SPARCL investigators have also performed an on-treatment analysis, in which they used LDL-C as a surrogate for adherence (Amarenco, P; personal communication). The analysis was based on 55,045 LDL-C measurements. The results were divided into 3 groups: no change or an increase in LDL-C (32.7%), a <50% decrease (39.4%), and a ≥50% decrease (27.9%). A total of 96% of the measurements corresponding to LDL-C reductions ≥50% were from patients treated with atorvastatin 80 mg. As well, 88% of the patients randomized to atorvastatin had at least one LDL-C measurement corresponding to a ≥50% reduction. The risk of all stroke was reduced by 31% in patients achieving an LDL-C reduction of ≥50%. In contrast, this endpoint decreased by only 11% when the reduction in LDL-C was <50%, which failed to achieve statistical significance. Ischemic stroke was reduced by 33% in the group with an LDL-C reduction of ≥50%, but by a non-significant 10% when the reduction was <50%. Similar findings were observed in the major coronary endpoints, which were reduced by 37% in the group with a ≥50% LDL-C reduction, but were unchanged in the other group.

In summary, patients considered to be most adherent to atorvastatin experienced the greatest reductions in CV events and ischemic stroke without an increase in hemorrhagic strokes (Figure 1). Atorvastatin 80 mg daily significantly reduces the risk of stroke and major coronary events in patients with recent stroke or TIA without known CHD. These results support the initiation of atorvastatin 80 mg daily in patients with stroke or TIA soon after the event.

Review of statin therapy in ACS

ACS occurs in the setting of plaque rupture and the presence of vascular inflammation. There is a high risk of recurrent events in the first few months. It is possible that the mechanisms whereby statins are beneficial in this condition are different than in patients with stable CHD or in primary prevention.

Figure 1: SPARCL on-treatment analysis



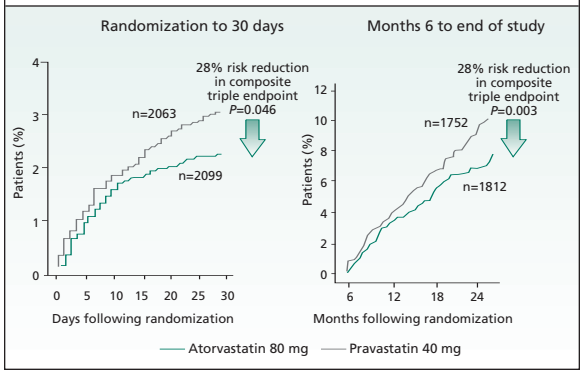
Note: Percent change effects from Cox proportional hazards models with adjustment for gender and baseline age with reference group = no change or increase

In fact, it takes about 6-8 months before the cumulative event curve in patients with ACS becomes parallel with that of stable CHD patients. Thus, it was particularly important to develop treatment modalities that could impact the high event rate in the early period after an ACS.

The MIRACL trial, published in 2001, was the first large clinical trial using a high-dose statin in patients with a recent ACS. This trial randomized 3,086 ACS patients immediately after their event to atorvastatin 80 mg or placebo. The patients were treated for 16 weeks and, at the end of this period, the mean LDL-C level was 1.8 mmol/L in the atorvastatin group and 3.4 mol/L in the placebo group. There was a 16.8% risk reduction in the composite primary endpoint (including death, nonfatal MI, cardiac arrest with resuscitation, and recurrent symptomatic myocardial ischemia requiring hospitalization) in patients treated with atorvastatin.[3]

It was not until the publication of the PROVE-IT trial that high-dose atorvastatin asserted its claim to become the standard of therapy in the management of ACS.[4] The reasons why clinical practice did not change until PROVE-IT may be understood by examining the findings of a recent meta-analysis of all the previous ACS statin trials. It included MIRACL, but not the more recently published PROVE-IT trial. In the evaluation of the hard clinical endpoint of death, non-fatal MI, and nonfatal stroke, the meta-analysis found only a nonsignificant risk reduction of 7% with statin treatment both at 1 and 4 months.[20] The PROVE-IT trial changed the approach to ACS patients in a more conclusive fashion. This study had both a sample size that was large enough and adequate endpoints to demonstrate the benefits of high-dose atorvastatin in ACS. It enrolled 4,162 patients hospitalized with an ACS whose average LDL-C was 2.74 mmol/L. Patients were randomized to receive either atorvastatin 80 mg or pravastatin 40 mg daily for a period of 18-36 months. The primary efficacy endpoint was a composite of death from any cause, MI, documented unstable angina requiring hospitalization, revascularization, and stroke. The end-of-treatment median LDL-C was 1.6 mmol/L in the patients treated with atorvastatin 80 mg and 2.46 mmol/L in the patients treated with pravastatin 40 mg. There was a 16% relative risk reduction in the primary endpoint in patients treated with atorvastatin compared to pravastatin treatment.[4]

Figure 2: PROVE-IT sub-analysis: CV benefits at 30 days and end of study†[21]



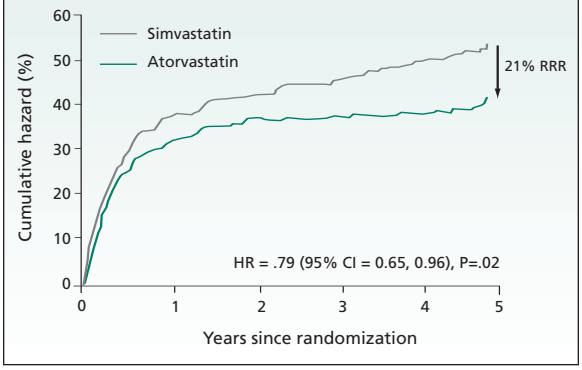
† Composite of death, MI, or rehospitalization with recurrent ACS

A recent post-hoc analysis of the trial studied the triple composite endpoint of death, MI, or rehospitalization with recurrent ACS. The outcomes were assessed in 2 periods: from randomization to 30 days, and from 6 months to the end of the study. Interestingly, the relative risk reduction in the composite endpoint with atorvastatin was 28% in both the early and late periods compared to pravastatin (Figure 2).[21] Treatment discontinuation rate was 13.8% for atorvastatin-treated patients and 10.9% for patients randomized to pravastatin. ALT elevations >3 times the upper limit of normal (ULN) occurred in 3.3% of atorvastatin patients and in 1.1% of pravastatin patients. There were no cases of rhabdomyolysis in either group.

The A to Z trial was also conducted in patients with ACS and compared simvastatin 40 mg and 80 mg versus placebo and simvastatin 20 mg in an early intensive versus a delayed conservative strategy. Patients were followed for 2 years and, although the primary endpoint was reduced by 11% with the early intensive strategy, this result did not achieve statistical significance.[11] There were problems with the study, including high dropout and crossover rates that likely influenced the results.

The IDEAL trial[13] enrolled patients with a previous MI who were randomized to simvastatin 20 or 40 mg versus atorvastatin 80 mg. The average LDL was 2.6 mmol/L in patients receiving simvastatin and 2.0 mmol/L in those receiving atorvastatin. The follow-up period was 5 years and the primary endpoint of major coronary events was reduced by a nonsignificant 11% with atorvastatin 80 mg compared with simvastatin 20 or 40 mg. In contrast, the softer endpoint of any CV event was reduced by 16% in the atorvastatin-treated group and this risk reduction achieved statistical significance ($p<0.001$).[13] As in previous trials, the use of atorvastatin 80 mg was safe and well-tolerated. There were no cases of myopathy defined as a total CPK >10 times the ULN on 2 consecutive occasions with muscle symptoms. It is important to emphasize that IDEAL enrolled most of its 8,888 patients in the stable phase after an MI. A subsequent analysis was performed in 999 patients who were enrolled in the study within 8 weeks of their index MI.

Figure 3: IDEAL ACS patients: any CV event MCE + Revasc + Stroke + TIA + UA + CHF + PAD[13]



In this subgroup, the more aggressive LDL-C lowering with atorvastatin 80 mg led to a 21% relative risk reduction in all CV events ($p = 0.02$; Figure 3; Pedersen T: personal communication).

In summary, in randomized controlled trials, atorvastatin exerts significant benefits in patients with ACS. MIRACL was a 16-week trial with atorvastatin 80 mg that demonstrated a 16% reduction compared to placebo in the risk of recurrent events. PROVE-IT was a 2-year trial with atorvastatin 80 mg versus pravastatin 40 mg that showed a 16% reduction in CV events. The IDEAL ACS subgroup analysis revealed a 21% reduction in CV events in post-MI patients randomized within 8 weeks to atorvastatin 80 mg compared to standard-dose simvastatin. The 5-year data represent the longest follow-up of ACS patients on statin therapy.

Review of atorvastatin safety data

Although not the first statin to be introduced, atorvastatin soon became the leading one, based on its efficacy. The first overview of its safety was published by Newman et al in 2003.[22] The analysis included 44 completed studies and 9416 atorvastatin-treated patients. There was a very low occurrence of persistent ALT or AST elevations (defined as a value >3 times ULN on 2 separate occasions within 14 days). The 10 mg and 20 mg doses of atorvastatin were associated with liver enzyme elevations of 0.13% and 0.12%, respectively, compared to 0.3% for placebo. The 40 mg dose was associated with 0.4% enzyme elevations, and even the 80 mg dose was safe since enzyme elevations occurred in only 0.89% of patients.

The results of AFCAPS/TexCAPS provide some context to these figures. An equivalent elevation in hepatic enzymes was seen in 0.6% of patients on lovastatin and 0.3% of patients on placebo and this difference did not achieve statistical significance.[15,23] Of note, of the 18 patients with consecutive enzyme elevations in the study, 14 resolved on treatment or had a negative rechallenge. This means that, of the 6,605 participants in the study who were followed for an average of 5.2 years, the statin was discontinued in only 4 patients.

It is important to note that cholesterol lowering itself may affect hepatocyte membranes and result in minor ALT/AST elevations; however, these elevations usually disappear with continued treatment and minor elevations are not predictive of significant liver dysfunction. The potentially serious complication of acute liver failure has, however, been reported with most cholesterol-lowering drugs, including the statins, but it is uncertain whether the rate is higher than background. Many experts suggest that monitoring hepatic enzymes is not necessary because of the rarity of acute liver failure and the poor predictive value of minor elevations.[24]

Myalgia is the adverse effect of the statins that patients are most likely to complain about. Nevertheless, it is also a relatively infrequent problem. In the previously discussed study by Newman et al, myalgia occurred in 2%-3% of patients taking atorvastatin and in 2% of those randomized to placebo. Even more interesting is the fact that the incidence of myalgia was not dose-dependent and was identical for both the 10 mg and the 80 mg dose of atorvastatin (3%).[22] The number of cases of statin-related rhabdomyolysis reported to the US Food and Drug Adminstration is extremely low for all of the statins (excluding cerivastatin).[25] As of 2002, there were only 73 cases out of 484 million prescriptions. Almost half were associated with cerivastatin (31 cases out of 9.8 million prescriptions),[25] 19 were reported with lovastatin (out of 99 million prescriptions), and 6 cases with atorvastatin (out of 140 million prescriptions). Thus, the reported rate was 0.19 per million prescriptions for lovastatin and 0.04 for atorvastatin. This corresponds to an excellent safety profile for atorvastatin and underscores the fact that cerivastatin was a clear anomaly, with a rate of 3.16 per million.

A retrospective review of a primary care practice found that 1,014 (85%) of 1,194 patients taking a statin had a monitoring test over the course of 1 year. Only 6 patients (0.9%) were identified with creatine kinase (CK) levels >5-times UNL, but the authors concluded that none appeared related to statin use and no documented adverse sequelae were identified related to the laboratory results. These authors also suggested that routine measurement of total CK was not necessary.[26]

As previously mentioned, the MIRACL study compared atorvastatin 80 mg versus placebo and found that an elevation in hepatic enzymes occurred in 2.5% and 0.6% of the patients, respectively. There was no difference, however, in myositis or in overall serious adverse events.[3] In the PROVE-IT study, the ALT elevation was 3.3% with atorvastatin 80 mg and 1.1% with pravastatin 40 mg ($p<0.001$). There was no difference between the 2 statins in CK elevation or in discontinuation for myalgias or elevated total CK.[4] The TNT study enrolled 10,000 patients with CHD randomized to either atorvastatin 80 mg or 10 mg who were followed for an average of 4.9 years. The incidence of treatment-related adverse events was 5.8% with atorvastatin 10 mg and 8.1% with atorvastatin 80 mg. There was no difference in the rate of treatment-related myalgia (4.7% versus 4.8%) or rhabdomyolysis. Consecutive elevations of AST/ALT occurred in 0.2% of patients receiving 10 mg and 1.2% of those on the dose of 80 mg.[12]

Table 1: Safety of atorvastatin 80 mg in clinical trials[27]

	Follow-up	Patients	↑ALT/AST >3x ULN*	↑CK >10 x ULN*
Newman et al*	variable	4,798	26 (0.6%)	2 (0.06%)
PROVE-IT	2 years	2,099	69 (3.3%)	NA
TNT	4.9 years	4,995	60 (1.2%)	0
IDEAL	4.8 years	4,439	61 (1.38%)	0
SPARCL	4.9 years	2,365	51 (2.2%)	2 (0.08%)
Total	variable	18,696	267 (1.43%)	4 (0.021%)

CK = creatine kinase; ULN = upper limit of normal
* Consecutive measurements except PROVE-IT

Altogether, 18,696 patients have received atorvastatin 80 mg in randomized clinical trials. Only 267 patients had consecutive elevations of ALT/AST that were >3 times ULN (1.43%). The incidence of CK elevation was much lower since only 4 patients were reported to have CK levels >10-times ULN (0.021%; Table 1).[27]

The clinical trials conducted with atorvastatin 80 mg were not designed with the numbers of patients necessary to assess a difference in total mortality. However, it is reassuring that, while studies like TNT and IDEAL demonstrated strong trends towards a reduction in CV mortality with atorvastatin 80 mg, there was no significant difference, nor was there a consistent trend for or against atorvastatin, in the rate of non-CV mortality.[12,13]

Further evidence to support the use of high-dose atorvastatin in appropriate patients comes from an analysis of the results of the TNT trial. When the patients are divided by quintiles (including 2,000 patients per quintile), according to their on-treatment LDL-C levels, interesting findings emerged. Patients in the lowest quintile had LDL-C levels ≤1.66 mmol/L (mean 1.4 mmol/L), while those in the highest quintile had on-treatment LDL-C levels >2.75 mmol/L (mean 3.16 mmol/L). The rate of major CV events was 7.7% in the lowest quintile and 11.9% in the highest quintile ($p<0.0001$). Non-CV deaths occurred in 2.2% of patients in the lowest quintile of LDL-C and in 2.7% of those in the highest quintile, thus providing additional evidence that more aggressive LDL-C reduction was not associated with a higher rate of serious adverse events (Table 2).[28]

It is clear from these data that atorvastatin 80 mg has an excellent safety profile. Given the realities of clinical practice, in which the presence of co-morbidities and concomitant medications must be considered, it is important to note that the risk of myopathy and rhabdomyolysis is increased in patients taking medications that are metabolized by the cytochrome P-450 3A4 and share this pathway with the statins. Examples include fibrates, niacin, cyclosporin, tacrolimus, protease inhibitors, verapamil, diltiazem, and macrolide antibiotics.

Table 2: TNT – The result of endpoints based on quintile of LDL-C[28]

On treatment	Quintile 1 N=1836	Quintile 2 N=1932	Quintile 3 N=1987	Quintile 4 N=2030	Quintile 5 N=1984
LDL-C range	≤1.66	1.66-1.99	1.99-2.33	2.33-2.75	>2.75
LDL-C mean	1.40	1.81	2.15	2.51	3.16
Major CVE*	7.7%	8.2%	9.2%	11.1%	11.9%
All deaths	4.5%	5.5%	5.7%	6.1%	5.2%
CV deaths	2.3%	2.2%	2.8%	3.1%	2.6%
Non-CV deaths	2.2%	3.3%	2.9%	3.1%	2.7%

* $p<0.0001$ for major cardiovascular events (CVE = CHD death, MI, resuscitated arrest, stroke

No increase in muscle complaints, suicide, hemorrhagic stroke or cancer deaths in Quintile 1

Conclusion

In conclusion, few other therapies have been studied as thoroughly in clinical trials as the statins. The evidence of their efficacy and safety is almost without parallel. Recent trials have shown the additional benefits of intensive lipid-lowering with high doses of potent statins on the progression of atherosclerosis and on clinical outcomes. The added benefits are accomplished without a significant compromise of the excellent safety and tolerability. Most of these trials have been conducted with the 80 mg dose of atorvastatin and have extended the already considerable benefits of the statins to patients in the early period following ACS and stroke.

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