The Intensive Statin Therapy Myth

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Abstract

Statins play an important role in the treatment and prevention of coronary artery disease and atherosclerosis. Currently, however, despite its important qualities, the use of statin therapy in the treatment of CAD patients ranges only between 30 and 60% in Europe, the United States and Israel. A wide gap still exists between the numerous scientific publications demonstrating the beneficial effects of statins and the low rate of implementing the guidelines in practice. A Medline search up to June 2005 on all prospective, double-blind, randomized clinical trials evaluating the impact of intensive statin therapy (any statin dose >40 mg/daily) on clinical outcomes after a 1 year follow-up revealed only eight trials. In all the eight trials, with a follow-up period of 12–60 months, intensive statin therapy was significantly more effective than and at least as safe as placebo or other standard statin regimens. Thus, based on the current evidence-based medicine, intensive statin therapy enables more patients with CAD to achieve the current National Cholesterol Education Program goal for low density lipoprotein, while ensuring a relatively high safety profile.

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Statins play an important role in the treatment and prevention of coronary artery disease and atherosclerosis [1]. They have proved effective in reducing morbidity and coronary as well as all-cause mortality [1–3] among patients with acute myocardial infarction. The need for coronary artery bypass surgery and coronary angioplasty and the rate of strokes and recurrent coronary events have also been reduced as a result of statin therapy.

Therapeutic lifestyle changes constitute an essential modality in clinical management. Currently, however, despite its important qualities, the use of statin therapy in the treatment of CAD patients (post-AMI, post CABG, post-angiography and post-stroke) ranges only between 30 and 60% in Europe, the United States and Israel [4–6]. Recently the Acute Coronary Syndromes Israeli Survey (ACSIS) 2002 trial, performed in all 26 intensive cardiac care units and 15 intermediate cardiac care units operating in Israel, registered that approximately 66% of all post-AMI patients discharged from these units were prescribed statin therapy. The number of those who actually took statins and reached a target low density lipoprotein cholesterol level below 100 mg/dl, as recommended by the National Cholesterol Education Program, Adult Treatment Panel III, is unknown and might even be considerably lower than 60%. The recently published NCEP report [7] suggests that in high risk persons, the recommended LDL-C goal is <100 mg/dl, but when risk is very high an LDL-C goal <70 mg/dl is a therapeutic option and a reasonable clinical strategy, including patients at very high risk who have a baseline LDL <100 mg/dl.

Records worldwide point to the fact that most patients taking statins do not meet their LDL-C goal, a fact also true for Israeli patients. Strict follow-up of patient compliance is lacking on the part of the medical community to ensure that patients prescribed statins reach their LDL-C goal, as set by the NCEP [1,7] and adopted by the Israel Heart Society and Israel Medical Association [8].

The aim of the current study is to review all prospective, double-blind, randomized clinical trials, achieved by a Medline search up to June 2005, evaluating the impact of intensive statin therapy (any statin dose >40 mg/daily) with at least 1 year follow-up on efficacy outcomes and safety.

Clinical trials

AVERT trial

The Aggressive Lipid-lowering Therapy Compared with Angioplasty in Stable Coronary Artery Disease (AVERT) trial provided a breakthrough regarding lipid-lowering regimens [9]. This prospective, double-blind trial showed that treatment with atorvastatin 80 mg daily for 18 months in symptomatic CAD patients with significant anatomic lesions in the coronary arteries was more efficient than balloon angioplasty in reducing ischemic events by a significant 36%. The group treated with atorvastatin 80 mg daily (the "conservative" treatment group) reached LDL-C

CAD = coronary artery disease
AMI = acute myocardial infarction
CABG = coronary artery bypass graft

NCEP = National Cholesterol Education Program
LDL-C = low density lipoprotein-cholesterol

levels of 70 mg/dl. There was no significant difference regarding side effects between the conservative treatment group and those who underwent balloon angioplasty during the 18 month follow-up.

MIRACL trial

The Effects of Atorvastatin on Early Recurrent Ischemic Events in Acute Coronary Syndromes (MIRACL) trial [10] evaluated treatment with atorvastatin 80 mg/day compared to placebo during 24–96 hours in patients with acute coronary syndrome (228 patients received atorvastatin and 269 placebo). A 16 week follow-up demonstrated a significant reduction in combined coronary events (mortality, AMI, cardiac arrest, and recurrent cardiac ischemia requiring hospitalization) in the atorvastatin-treated group, where a mean LDL-C of 72 mg/dl was observed. Adverse events (elevated liver enzymes more than three times upper normal levels or elevation of creatine phosphokinase more than 10 times UNL) were indeed higher in the atorvastatin group compared to placebo (2.5% vs. 0.6%); however, these results should be looked at in the setting of critical patients with acute coronary syndromes.

ASAP trial

The Effect of Aggressive versus Conventional Lipid Lowering on Atherosclerosis Progression in Familial Hypercholesterolemia (ASAP) trial [11] included 325 patients with familial hypercholesterolemia. Approximately half (160 patients) received atorvastatin 80 mg daily and the remaining 165 patients simvastatin 40 mg daily. The study endpoint was to compare patients' anatomic carotid intima-media thickness over a 2 year follow-up. LDL-C levels were reduced by 50% in the atorvastatin group compared to 41% in the simvastatin group. After a 2 year follow-up, IMT was significantly reduced in the atorvastatin group but had increased in the simvastatin group. Adverse effects were rare and similar in both groups.

ARBITER trial

The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) trial [12] included 161 patients (46% with CAD) and demonstrated significant IMT reduction during a 12 month atorvastatin 80 mg daily treatment (mean LDL-C 76 mg/dl) compared to pravastatin 40 mg daily (mean LDL-C 110 mg/dl), with no differences in adverse reactions between the two groups.

PROVE IT trial

The Comparison of Intensive and Moderate Lipid Lowering with Statins Following Acute Coronary Syndrome (PROVE IT) trial [2,13] was a 2 year prospective, double-blind, multi-center study that compared treatment with atorvastatin 80 mg daily to pravastatin 40 mg daily in 4,162 patients with acute coronary syndrome. The study, although originally planned for a non-inferiority of pravastatin compared to atorvastatin, demonstrated a significant 16% reduction in mortality and re-infarction with intensive atorvastatin treatment (with LDL-C treatment of 62 mg/dl) compared to standard pravastatin therapy (and LDL-C treatment 95 mg/dl). As in previous studies, this trial also failed to demonstrate any differences in adverse effects between intensive and standard statin strategies.

REVERSAL trial

The recently published Effect of Intensive Compared with Moderate Lipid-lowering Therapy on Progression of Coronary Atherosclerosis (REVERSAL) trial [3,14] compared the efficacy of atorvastatin and pravastatin using exactly the same dose as in the PROVE IT trial (80 mg daily and 40 mg daily, respectively) in patients with stable angina pectoris and atherosclerotic lesions in the coronary vessels. Intensive 18 month atorvastatin therapy (with LDL-C treatment 79 mg/dl) significantly reduced the atheroma volume observed on intracoronary ultrasound, compared to the standard pravastatin therapy (with LDL-C 110 mg/dl), again without any significant differences in adverse events between the two groups.

In addition, Newman et al. [15] reviewed 44 controlled trials with 16,495 dyslipidemic patients, of whom 9,416 were treated with atorvastatin in various doses, 1,789 received placebo and 5,290 received other statins. They could not demonstrate any atorvastatin dose-dependent adverse events; also, no differences in atorvastatin- or other statin-induced adverse events were observed. The total number of adverse events was very low: a rise in liver function tests >3 UNL occurred in 0.5% of patients, while CPK >10 UNL occurred in one patient only and there was no clinical myopathy and/or rhabdomyolysis).

A to Z trial

In the international, randomized, double-blind Aggrastat-to-Zocor (A to Z) study of patients with acute coronary syndrome, 2,232 patients received placebo for 4 months followed by 20 mg simvastatin per day and 2,265 patients received simvastatin 40 mg per day for 1 month followed by 80 mg thereafter in phase Z of the A to Z trial [16]. Among the patients in the placebo plus simvastatin group, the median LDL-C achieved while taking placebo was 122 mg/dl at 1 month and 77 mg/dl at 8 months while taking 20 mg/day simvastatin. Among the patients in the simvastatin only group, the median LDL-C achieved at 1 month while taking 40 mg/day simvastatin was 68 mg/dl and 63 mg/dl at 8 months while taking 80 mg/day simvastatin. A total of 343 patients (16.7%) in the placebo plus simvastatin group experienced the primary endpoint (composite of cardiovascular death, non-fatal myocardial infarction, readmission for acute coronary syndrome and stroke) compared with 309 (14.4%) in the simvastatin-only group (40 mg/80 mg) ($P = 0.14$). Cardiovascular death occurred in 109 (5.4%) and 83 (4.1%) patients in the two groups ($P = 0.05$). No difference was evident in the first 4 months be-

UNL = upper normal levels
IMT = intima-media thickness

CPK = creatine phosphokinase

tween the groups for primary endpoint, but from 4 months until the end of the study the primary endpoint was significantly reduced in the simvastatin-only group ($P = 0.02$).

Myopathy (CPK>10 times the UNL associated with muscle symptoms) occurred in nine patients (0.4%) receiving simvastatin 80 mg/day, in no patients receiving lower doses of simvastatin, and in one patient receiving placebo ($P = 0.02$).

TNT trial

Recently, LaRosa and co-workers [17] demonstrated in a randomized, prospective double-blind study with a median follow-up of 4.9 years that intensive lipid-lowering therapy with 80 mg atorvastatin per day in 4,995 patients with stable CAD and LDL-C less than 130 mg/dl provided significant clinical benefit (i.e., the occurrence of a first major cardiovascular event, defined as death from CAD, non-fatal non-procedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or non-fatal stroke) beyond that afforded by treatment with 10 mg atorvastatin per day in 5,006 patients. A primary event occurred in 434 patients (8.7%) receiving 80 mg atorvastatin, as compared with 548 patients (10.9%) receiving 10 mg atorvastatin, representing an absolute reduction in the rate of major cardiovascular events of 2.2% and a 22% relative reduction in risk (hazard ratio 0.78, 95% confidence interval 0.69–0.89, $P < 0.001$). As compared with a 10 mg dose of atorvastatin, intensive therapy with high dose atorvastatin reduced the risk of stroke by 23%. However, there was no difference between the two treatment groups in overall mortality. The mean LDL-C levels were 77 mg/dl during treatment with 80 mg atorvastatin and 101 mg/dl during treatment with 10 mg atorvastatin. The incidence of persistent elevations in liver aminotransferase levels was 0.2% in the group given 10 mg atorvastatin and 1.2% in the group given 80 mg atorvastatin ($P < 0.001$). Treatment-related myalgia was reported by 241 patients (4.8%) in the group given 80 mg atorvastatin and by 234 patients (4.7%) in the group given 10 mg atorvastatin ($P = 0.72$). There were no persistent elevations in CPK (defined as two consecutive measurements obtained 4–10 days apart that were more than 10 times the UNL range). Five cases of rhabdomyolysis were reported (two in the group given 80 mg atorvastatin and three in the group given 10 mg atorvastatin). The clinical benefit of reducing LDL-C levels substantially below 100 mg/dl extended beyond the CAD-related vasculature. The findings regarding drug safety are consistent with the adverse-event profiles of these two doses of atorvastatin reported in other large-scale trials of atorvastatin [13,15].

Discussion

In all the eight prospective, double-blind, randomized clinical trials evaluating the impact of intensive statin therapy (any statin dose >40 mg/daily) on efficacy outcomes and safety, with a follow-up period of 12–60 months, intensive statin therapy was significantly more effective and as safe as placebo or other standard statin regimens [Table 1].

A decade has passed since the first publication, the 4S study [18], established the usefulness of statin therapy in post-AMI patients. However, a wide gap still exists between the numerous scientific publications demonstrating the beneficial effects of statins and the low rate of implementing the guidelines in

Table 1. Key findings of clinical trials with intensive statin therapy

Key findings	AVERT [9]	MIRACL [10]	ASAP [11]	ARBITER [12]	PROVE-IT [13]	REVERSAL [14]	A to Z [16]	TNT [17]
No. of patients (statin/placebo vs. intensive/moderate statin)	341 (164/177)	138 (68/70)	325 (160/165)	3086 (1538/1548)	4162 (2099/2063)	502 (253/249)	4497 (2232/2265)	10,001 (4995/5006)
Statin used and dose (mg/day)	A 80 vs. angio	A 80 vs. P 40	A 80 vs. S 40	A 80 vs. P 40	A 80 vs. P 40	A 80 vs. P 40	Placebo+S 20 vs. S 40+S 80	A 80 vs. A 10
Clinical indication for therapy	Stable CAD	Hyperlipidemic patients (46% stable CAD)	Familial hypercholesterolemia	ACS	ACS	Stable CAD	ACS	Stable CAD
Mean length of follow-up (months)	18	12	24	4	24	18	24	59
LDL-C baseline (mg/dl)	146	151	314	124	106	150	122	152
LDL-C during trial: Statin/placebo vs. intensive/moderate statin (mg/dl)	77/119	76/110	150/186	72/135	62/95	79/110	77/63	77/101
Percent LDL-C change statin/placebo vs. intensive/moderate statin at study end	-46/-18	-49/-27	-51/-41	-40/+12	-42/-10	-46/-26	-36/-48	-49/-34
Percent alanine aminotransferase elevation (>3 UNL) statin/placebo vs. intensive/moderate statin	2.4/0	0/0	0/0	2.5/0.6	3.3/1.1	2.3/1.6	0.4/0.9	1.2/0.2
Percent aspartate aminotransferase elevation (>3 UNL) statin/placebo vs. intensive/moderate statin	0/0	0/0	0/0	NA	0/0	0.6/0.6	0.4/0.9	1.2/0.2
Percent CPK (>10 UNL) statin/placebo vs. intensive/moderate statin	0/0	0/0	0/0	NA	3.3/2.7	0/0	0.04/0.4	0/0
Percent rhabdomyolysis	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0.04/0.06

A = atorvastatin, ACS = acute coronary syndrome, NA = not available, P = pravastatin, S = simvastatin

practice. One explanation may be the relatively low statin dose prescribed to CAD patients in Israel. While most large controlled studies were conducted with statin doses of at least 40 mg/day (e.g., CARE [19], LIPID [20], Heart Protection Study [21]), or with doses 20–40 mg/day (e.g., the 4S study [18]), it is "acceptable" and common practice in Israel, despite lack of solid evidence, to administer statin therapy for CAD patients with an initiating dose of only 10 mg/day.

It is known that not all the beneficial effects of statin therapy are attributable to its lipid-lowering characteristic, but rather to its non-lipid lowering ("pleiotropic") effects, which include reducing inflammation, stabilizing atherosclerotic plaque, lowering C-reactive protein levels and improving endothelial dysfunction and antithrombotic and anti-platelet qualities [22,23].

An additional commonly accepted, over-exaggerated, unexplained phenomenon regarding statin administration in Israel is the fear of statin-induced liver toxicity and rhabdomyolysis. A careful review of all large randomized, double-blind, placebo-controlled and prospective clinical trials with statins in CAD patients revealed that adverse events from statin administration are extremely low, ranging between 0.4 and 1.5%, similar to that of placebo [1–3,19–21,24]. As a result of these findings, it is difficult to understand why almost 60% of CAD patients receiving statin therapy are not treated according to the current NCEP guidelines.

Recently, it has even been suggested in some well-controlled, evidence-based studies that the current NCEP LDL-C goal for CAD patients should be updated [7]. These studies call upon intensive (or even "aggressive") lowering of LDL-C levels, even beyond the NCEP guidelines, reaching 70–80 mg/dl [24]. The current NCEP guidelines discuss LDL goal achievement and do not recommend the routine use of statins above 40 mg/daily to all CAD patients. Our group was among the first [25] to show that intensive lowering of LDL-C levels to below 100 mg/dl in CAD patients, reaching a mean of 75 mg/dl, improves endothelial dysfunction in the brachial artery. We demonstrated a direct correlation between the lowering of LDL-C levels to below 100 mg/dl in patients with CAD and improvement of endothelial dysfunction in the brachial artery in these patients [25]. The Post-CABG Trial [26] also calls for lowering LDL-C levels to below 100 mg/dl in patients undergoing vein graft surgery.

In his editorial on the TNT trial, Pitt [27] expresses concern regarding the non-significant difference in mortality from non-cardiovascular causes between high dose and low dose statin treatment. Cannon and team [28] suggested that this difference may be due to chance. They compared intensive and standard lipid lowering with respect to mortality from cardiovascular and non-cardiovascular causes in three separate trials (PROVE IT [13], A to Z [16] and TNT [17]), in which mortality from cardiovascular causes was significantly reduced by 24% (P = 0.004), adding further support to the trend toward reduced mortality from cardiovascular causes seen with intensive statin therapy. This analysis, according to Cannon's group [28], should provide reassurance that intensive lipid-lowering does not appear to have any adverse effect on mortality from non-cardiovascular causes, and that in fact it is associated with substantial benefit in preventing morbidity and mortality from cardiovascular causes.

Conclusion

In all eight prospective randomized clinical trials with a follow-up period of 12–60 months reviewed here [Table 1], we found that intensive statin therapy was significantly more effective than and at least as safe as placebo or other standard statin regimens. Thus, based on these results, a more intensive statin therapy is recommended to better achieve the current suggested LDL-C NCEP goal, while ensuring a relatively high safety profile.

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