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Atorvastatin

Pharmacological Characteristics and Lipid-Lowering Effects

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Abstract

By inhibiting 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase, the statins reduce hepatocyte cholesterol levels, which results in up-regulation of low-density lipoprotein (LDL) receptors and, consequently, increased clearance of LDL-cholesterol (LDL-C) from the plasma. Structural differences among the available statins partially account for differences in their capacity to inhibit HMG-CoA reductase and their lipid-lowering efficacy, and for variability in other biological properties, such as their pharmacokinetic characteristics and their tolerability and propensity to interact with other drugs. In terms of pharmacokinetic properties, the synthetic (type II) HMG-CoA analogue atorvastatin exhibits a number of characteristics that are different to those of other members of the class, including a longer plasma half-life and metabolites that have an ability to inhibit HMG-CoA reductase equivalent to that of the parent drug. These characteristics are postulated to be responsible for a more prolonged inhibition of HMG-CoA reductase, and, hence, for the greater efficacy of atorvastatin in decreasing total and LDL-C levels relative to other statins (with the exception of rosuvastatin) noted in clinical trials in patients with dyslipidaemias. From the available clinical trial data, atorvastatin can be considered one of the most effective statins, not only by taking into account its effects on LDL-C and ability to meet recommended treatment guidelines for this parameter, but also its effect on triglyceride levels and capacity to modify lipoprotein composition in a non-atherogenic manner.

Clinical studies with atorvastatin have also shed some light on the question as to whether it is better to focus on obtaining maximal reduction of LDL-C in at-risk patients or on cardiovascular outcomes. Cardiovascular event rates have been shown to be substantially lower in patients attaining LDL-C levels between 1.0 and 1.6 mmol/L (40–60 mg/dL) or ≤1.0 mmol/L (≤40 mg/dL) compared with higher levels (>2.1–2.6 mmol/L [>80–100 mg/dL]). This finding reinforces the update of the National Cholesterol Education Programme's clinical practice guidelines, which recommend LDL-C levels <2.6 mmol/L (100 mg/dL) to be the goal of antihyperlipidaemic drug therapy in high-risk patients with CHD, with an optional therapeutic target of <1.8 mmol/L (70 mg/dL) in patients at very high risk.

Since their introduction in the late 1980s, the 3-hydroxy-3-methylglutaryl coenzyme-A (HMG-CoA) reductase inhibitors (statins) have established a prominent place in therapeutics as a class of drugs

that can achieve relatively large reductions in plasma cholesterol levels and, thereby, ameliorate vascular atherosclerosis and reduce cardiovascular morbidity and mortality. These beneficial effects result from their ability to reduce endogenous cholesterol biosynthesis and increase the expression of low-density lipoprotein (LDL) receptors, which are responsible for LDL-cholesterol (LDL-C) uptake and clearance from plasma.[1,2] However, the statins vary in their pharmacological characteristics and dose-related efficacy in reducing LDL-C.[3] This review discusses the pharmacological characteristics of the statins, focusing on atorvastatin and its differences and similarities to other members of the class. In addition, it examines the clinical evidence with atorvastatin relating its effectiveness in improving individual lipid parameters, notably elevated LDL-C levels, in patients at increased risk of cardiovascular events.

1. Pharmacological Characteristics

The statins act by inhibiting the enzyme (HMG-CoA reductase) responsible for catalysing the conversion of 3-hydroxy-3-methylglutarate to mevalonate, which is an early rate-limiting step in the biosynthesis of cholesterol. By inhibiting HMG-CoA reductase, these drugs reduce hepatocyte levels of cholesterol, which results in up-regulation of LDL receptors and, consequently, increased clearance of LDL-C from plasma.[1,4] In addition to significantly lowering LDL-C levels, statins also cause smaller reductions in triglyceride levels, and minor increases in levels of high-density lipoprotein-cholesterol (HDL-C).[1]

1.1 Molecular Differences among the Statins

Although the statins have a common mechanism of action, there are some important differences in pharmacological characteristics among the class. To comprehend these differences, it is important to focus initially upon their diverse chemical structures. Statins can be divided into two subtypes: natural or fungally derived analogues (lovastatin, simvastatin and pravastatin; type I statins) and synthetic analogues (atorvastatin, fluvastatin and rosuvastatin; type II statins). While the chemical structures of the natural statins are very similar, the synthetic statins are considerably different from each other and from the natural statins (figure 1).[2,5]

All statins share a common mevalonate-like pharmacophore (dihydroxy heptanoic or heptenoic acid side chains) that is responsible for competitive inhibition of HMG-CoA reductase. Crystallography studies have highlighted the catalytic portion of the enzyme, and indicated that the HMG-like portion of each statin occupies the HMG binding site of the enzyme. As well as bonds formed through the HMG-like portions, each statin has different types of additional binding sites depending on their structural configuration. Natural statins, such as simvastatin, are, for instance, capable of forming bonds via the decalin ring structure, whereas synthetic statins, such as atorvastatin, feature a fluorophenyl group capable of forming different bonds (figure 2). These structural differences among the statins partially account for the differences in their capacity to inhibit HMG-CoA reductase enzyme and their lipid-lowering efficacy.[6-8] In addition, the other substituents of the statin molecules lead to variability in other biological properties and contribute to actions that are independent of HMG-CoA reductase inhibition and the lipid-lowering effect.[6] There are, for example, marked differences in their lipophilicity, absorption, plasma protein binding and elimination (table I), as well as in their tolerability and propensity to interact with other drugs.[1,6]

1.2 Pharmacokinetic Characteristics of Atorvastatin

Among the statins, atorvastatin exhibits a number of pharmacokinetic characteristics that are different to the other members of the class (table I). For example, it is the only statin with a metabolite that has an ability to inhibit HMG-CoA reductase equivalent to that of the parent drug. After administration, atorvastatin is extensively metabolised to ortho- and para-hydroxylated derivatives and various β-oxidation products,[10] and around 70% of the HMG-CoA reductase inhibition achieved with atorvastatin has been ascribed to its ortho- and para-

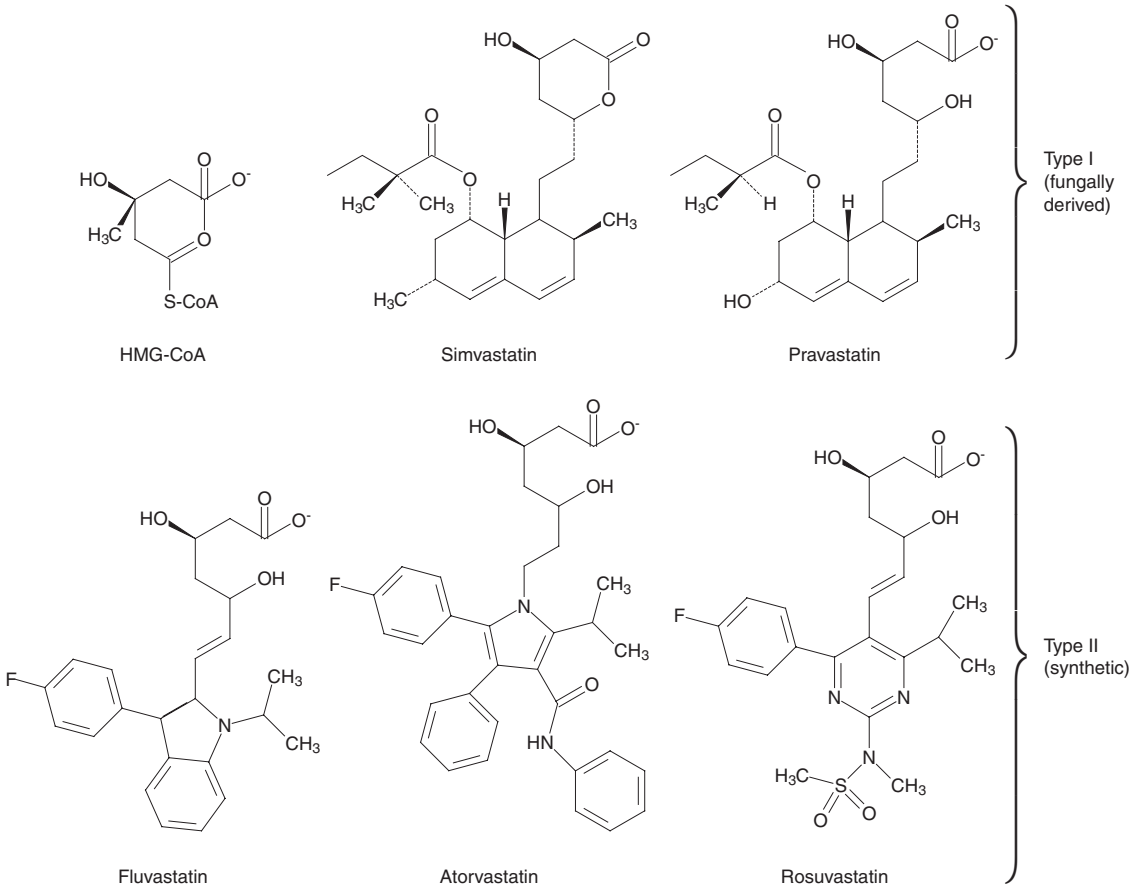

Fig. 1. Molecular configurations of the natural (fungally derived) and synthetic statins, showing their bidimensional structures (reproduced from Davidson and Toth,[5] with permission). **HMG** = 3-hydroxy-3-methylglutaryl.

hydroxylated metabolites.[4] Both atorvastatin and its metabolites are principally eliminated through biliary excretion, with only small amounts excreted in the urine. The elimination half-life of atorvastatin is approximately 14 hours, which is considerably longer than that of most other statins (with the exception of rosuvastatin) [table I], but the half-life of HMG-CoA reductase inhibition is around 20–30 hours as a result of the action of its active metabolites.[11] This long half-life has an important impact on drug administration schedules; whereas atorvastatin can be administered at any time during the day, most other statins – due to their shorter elimination half-lives – are administered in the evening to achieve the highest lipid-lowering effect possible.

2. Lipid-Lowering Efficacy of Atorvastatin

In patients with primary hypercholesterolaemia, atorvastatin has proven to be more effective in reducing total cholesterol, LDL-C and triglyceride levels when compared with equivalent milligram doses of simvastatin, lovastatin, fluvastatin and pravastatin. In the majority of comparative clinical trials, the efficacy of atorvastatin in dosages of 10 and 20 mg/day was equivalent to or better than that of dosages of 20 and 40 mg/day of these statins.[4]

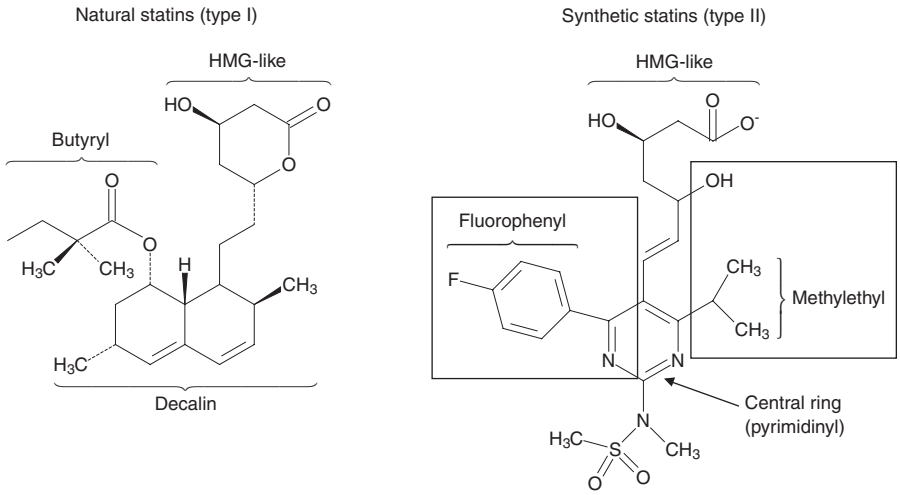

Fig. 2. Intermolecular differences between natural and synthetic statins (reproduced from Istvan,[7] with permission). **HMG** = 3-hydroxy-3-methylglutaryl.

In CURVES (The Comparative Dose Efficacy Study of Atorvastatin Versus Simvastatin, Pravastatin, Lovastatin, and Fluvastatin in Patients with Hypercholesterolemia), a randomised, open-label, 8-week study comparing atorvastatin with pravastatin, simvastatin, fluvastatin and lovastatin in 534 hypercholesterolaemic patients,[12] atorvastatin in dosages ranging from 10 to 80 mg/day proved to have a significantly greater capacity to reduce LDL-C and total cholesterol levels than equivalent milligram dosages of the other statins ($p \leq 0.01$) [table II]. Reductions in LDL-C levels achieved with atorvastatin dosages of 10, 20, 40 and 80 mg/day were 38%, 46%, 51% and 54%, respectively. Compared with atorvastatin 20 mg/day, reductions in LDL-C levels with the maximum dosages of pravastatin, simvastatin and fluvastatin permitted in the study (40 mg/day) were significantly lower ($p \leq 0.01$) [table II].[12]

These data are consistent with the results of the CHALLENGE trial, which was a randomised, open-label, 6-week comparison of atorvastatin 10 or 80 mg/day with simvastatin 20 or 80 mg/day in 1732 patients with dyslipidaemia with or without coronary heart disease (CHD).[13] Atorvastatin induced significantly greater reductions in the levels of LDL-C than simvastatin at both the minimum and maximum dosages (37.1% vs 35.4%, $p = 0.0097$ and 53.4% vs 46.7%, $p < 0.0001$, respectively). Atorvastatin 10 mg/day and 80 mg/day also produced significantly greater reductions in the levels of total cholesterol, triglycerides, very low-density lipoprotein cholesterol (VLDL-C) and apolipoprotein B (apoB) than simvastatin 20 and 80 mg/day (all $p < 0.05$), and a higher proportion of patients receiving atorvastatin reached the therapeutic goals in terms of LDL-C defined by the US National Cholesterol Education Panel (NCEP) in comparison with those receiving simvastatin.[13]

In ACCESS (Atorvastatin Comparative Cholesterol Efficacy and Safety Study), a randomised, 54-week trial comparing the efficacy of atorvastatin 10 mg/day titrated up to 80 mg/day with four other statins (simvastatin 10–40 mg/day, pravastatin 10–40 mg/day, fluvastatin 20–80 mg/day and lovastatin 20–80 mg/day) in 3916 hypercholesterolaemic patients both with and without a history of CHD,[14] atorvastatin achieved the greatest mean reduction in LDL-C levels at both 6 and 54 weeks. LDL-C levels were decreased by 36% and 42% at these times with atorvastatin, as compared with 19–30% at 6 weeks and 28–36% at 54 weeks with the other statins. The percentages of patients reaching the NCEP-recommended LDL-C goal levels, which were set on the

Table I. Clinical pharmacological characteristics of the available statins[1-3,9]

Characteristic	Atorvastatin	Lovastatin	Simvastatin	Pravastatin	Fluvastatin	Rosuvastatin
Origin	Synthetic	Microbial	Semisynthetic	Semisynthetic	Synthetic	Synthetic
Racemate	No	No	No	No	Yes	No
Prodrug	No	Yes	Yes	No	No	No
Solubility (C log P)	Lipophilic (4.1)	Lipophilic (4.3)	Lipophilic (4.7)	Hydrophilic (−0.2)	Lipophilic (3.2)	Hydrophilic (−0.3)
Absorption (%)	30	31	60–85	35	98	20
t_{max} (h)	2–4	2.8	1.3–2.4	0.9–1.6	0.5–1.5	3
Bioavailability (%)	12	<5	<5	17	10–35	75
Effect of food on bioavailability (% change)	Yes (↓ 13%)	Yes (↑ 50%)	No	Yes (↓ 30%)	Yes (↓ 15–25%)	No
Hepatic extraction (% absorbed dose)	>70	>70	78–87	66	68	90
Protein binding (%)	>98	95	95	48	>99	90
$t_{½}$ (h)	11–30	2.5–3	1.9–3	0.8–3	0.5–2.3	20
Renal excretion (%)	2	30	13	60	6	10
Metabolites contributing to lipid-lowering effect	Active	Yes	Yes	Yes; mainly inactive	Yes; mainly inactive	No
IC_{50} (nmol/L)[a]	15.2	2.7–11.1	18.1	55.1	17.9	12
Equipotent dosage	10	40	20	40	80	NA
Dosage range (mg/day)	10–80	10–80	5–80	5–40	20–80	5–40

a Inhibition of HMG-CoA reductase.

C log P = logarithm of the partition coefficient based on octanol/water phase; **HMG-CoA** = 3-hydroxy-3-methylglutaryl coenzyme-A; **IC_{50}** = 50% inhibitory concentration; **NA** = not available; **$t_{½}$** = terminal elimination half-life; **t_{max}** = time to reach peak plasma concentration; ↓ and ↑ denote decrease and increase, respectively.

Table II. Mean percentage changes (± SD) from baseline in lipid parameters in 534 hypercholesterolaemic patients (pts) who received 8 weeks' treatment with various dosages of atorvastatin, pravastatin, simvastatin, fluvastatin and lovastatin (CURVES study) [reproduced from Jones et al.,[12] with permission]

Drug	Dosage (mg/day)	No. of pts	LDL-C	TC	TG	HDL-C
Atorvastatin	10	73	−38 (10)	−28 (9)	−13 (25)	+5.5 (12)
	20	51	−46 (8)	−35 (6)	−20 (25)	+5.1 (11)
	40	61	−51 (10)	−40 (8)	−32 (19)	+4.8 (12)
	80	10	−54 (9)	−42 (7)	−25 (22)	−0.1 (9)
Pravastatin	10	14	−19 (14)**	−13 (12)**	+3 (46)	+9.9 (13)
	20	41	−24 (9)**,†	−18 (7)**	−15 (7)	+3.0 (8)
	40	25	−34 (9)**,‡	−24 (7)**	−10 (22)*	+6.2 (11)
Simvastatin	10	70	−28 (12)**	−21 (9)**	−12 (30)	+6.8 (9)
	20	49	−35 (11)**	−26 (8)**	−17 (22)	+5.2 (10)
	40	61	−41 (13)**,‡	−30 (10)**	−15 (29)*	+9.6 (13)*
Fluvastatin	20	12	−17 (8)**,†	−13 (6)**	−5 (32)	+0.9 (8)
	40	12	−23 (10)**,†,‡	−19 (9)**	−13 (3.4)*	−3.0 (10)
Lovastatin	20	16	−29 (13)**,†	−21 (9)**	−12 (23)	+7.3 (12)
	40	16	−31 (7)**,†,‡	−23 (6)**	−2 (27)**	+4.6 (13)
	80	11	−48 (8)	−36 (6)	−13 (28)	+8.0 (13)

CURVES = The Comparative Dose Efficacy Study of Atorvastatin Versus Simvastatin, Pravastatin, Lovastatin, and Fluvastatin in Patients with Hypercholesterolemia; **HDL-C** = high-density lipoprotein cholesterol; **LDL-C** = low-density lipoprotein cholesterol; **TC** = total cholesterol; **TG** = triglycerides; * $p \leq 0.05$, ** $p \leq 0.01$ vs atorvastatin at equivalent milligram dosage (Dunnett's test of significance); † $p \leq 0.02$ vs atorvastatin 10 mg/day; ‡ $p \leq 0.01$ vs atorvastatin 20 mg/day.

basis of patient risk categories, were significantly higher with atorvastatin (average for all categories 76%) than with simvastatin, pravastatin, fluvastatin and lovastatin (34–58%). In addition, reductions in triglycerides at 6 and 54 weeks were greater with atorvastatin (18% and 19%, respectively) than with any of the other statins, but there were no major differences in HDL-C level increases at 6 and 54 weeks of therapy between the treatments.[14]

Similarly, the results of ASSET (Atorvastatin vs Simvastatin Safety and Efficacy Trial), a randomised, treat-to-target trial in 1424 patients with mixed dyslipidaemia with or without type 2 diabetes mellitus, atorvastatin 10 mg/day was more effective than simvastatin 10 mg/day in reducing lipid parameters over a period of 6 weeks.[15] Compared with simvastatin, atorvastatin produced significantly greater ($p < 0.0001$) reductions in LDL-C (37.2% vs 29.6%), total cholesterol (27.6% vs 21.5%) and triglyceride (22.1% vs 16.0%) levels, while HDL-C levels were increased to a similar extent in the two treatment groups (7.4% vs 6.9%). As with ACCESS,[14] a significantly larger number of patients reached LDL-C goals with atorvastatin than with simvastatin (55.6% vs 38.4%; $p < 0.0001$).[15]

A meta-analysis of 164 short-term, randomised, placebo-controlled trials encompassing approximately 24 000 patients treated with statins and 14 000 placebo recipients compared the lipid-lowering effects of six available statins, including rosuvastatin.[16] At the upper dosage level of 80 mg/day, atorvastatin produced a substantially greater reduction in LDL-C levels (55%) than pravastatin (33%), simvastatin (42%), fluvastatin (33%) or lovastatin (45%), and only a slightly lower reduction than rosuvastatin (58%) [table III]. Other trials in which atorvastatin has been compared with rosuvastatin, such as the COMETS (COmparative study with rosuvastatin in subjects with METabolic Syndrome), RADAR (Rosuvastatin and Atorvastatin in different Dosages And Reverse cholesterol transport) and STELLAR (Statin Therapies for Elevated Lipid Levels compared Across dose ranges to Rosuvastatin) studies,[17-19] have also reported larger reductions in LDL-C levels with rosuvastatin, but near-equivalence of the two agents in terms of the proportions of patients achieving NCEP-recom-

Table III. Absolute reductions[a] (mmol/L, with 95% confidence intervals) and percentage reductions[b] in low-density lipoprotein cholesterol (LDL-C) levels achieved with statin drugs at various dosages: summary estimates from 164 randomised, placebo-controlled trials (reproduced from Law et al.,[16] with permission)

Statin	Daily dosage				
	5mg	10mg	20mg	40mg	80mg
Atorvastatin	1.51 (1.28, 1.74) [31%]	1.79 (1.62, 1.97) [37%]	2.07 (1.90, 2.25) [43%]	2.36 (2.12, 2.59) [49%]	2.64 (2.31, 2.96) [55%]
Pravastatin	0.73 (0.54, 0.92) [15%]	0.95 (0.83, 1.07) [20%]	1.17 (1.10, 1.23) [24%]	1.38 (1.31, 1.46) [29%]	1.60 (1.46, 1.74) [33%]
Simvastatin	1.08 (0.93, 1.22) [23%]	1.31 (1.22, 1.40) [27%]	1.54 (1.46, 1.63) [32%]	1.78 (1.66, 1.90) [37%]	2.01 (1.83, 2.19) [42%]
Fluvastatin	0.46 (0.18, 0.75) [10%]	0.74 (0.55, 0.93) [15%]	1.02 (0.90, 1.13) [21%]	1.30 (1.19, 1.41) [27%]	1.58 (1.40, 1.76) [33%]
Lovastatin	Not reported	1.02 (0.71, 1.34) [21%]	1.40 (1.21, 1.59) [29%]	1.77 (1.60, 1.94) [37%]	2.15 (1.86, 2.43) [45%]
Rosuvastatin	1.84 (1.74, 1.94) [38%]	2.08 (1.98, 2.18) [43%]	2.32 (2.20, 2.44) [48%]	2.56 (2.42, 2.70) [53%]	2.80 (2.63, 2.97) [58%]

a Absolute reductions are standardised to usual LDL-C levels of 4.8 mmol/L before treatment (mean concentrations in trials).

b Percentage reductions are independent of pretreatment LDL-C level.

mended LDL-C levels was observed. For example, in the STELLAR trial,[19] 85.2% of patients achieved NCEP goals with atorvastatin 40 mg/day as compared with 89.2% with rosuvastatin 40 mg/day. This trial also reported comparable reductions in triglyceride levels with the two drugs (18–35% for atorvastatin over the dosage range of 10–80 mg/day vs 18–26% for rosuvastatin over the dosage range 5–40 mg/day).[19]

Although the combination of ezetimibe with simvastatin has been shown to be more effective in lowering LDL-C levels than simvastatin monotherapy,[20] this was not found to be the case with atorvastatin monotherapy when data were considered across a broad dosage range. The VYVA (VYtorin Versus Atorvastatin) trial[21] reported that the proportion of patients achieving NCEP-defined LDL-C goals with different ezetimibe/simvastatin combinations (10mg/10mg, 10mg/20mg, 10mg/40mg or 10mg/80mg) were higher than with corresponding atorvastatin dosages, but the percentages of patients achieving the recommended goals did not seem to differ greatly when comparisons were made with 'equivalent' dosages of the two regimens, e.g. 87.6% of ezetimibe/simvastatin 10/20 mg/day recipients versus 85.3% of patients treated with atorvastatin monotherapy at a dosage of 40 mg/day.[21]

The greater efficacy of atorvastatin in decreasing total cholesterol and LDL-C levels as compared with other HMG-CoA reductase inhibitors (with the exception of rosuvastatin) is presumed to be due to a longer duration of HMG-CoA reductase inhibition associated with the comparatively long half-life of the drug[22,23] rather than to differences in the degree of enzyme inhibition.[4] Atorvastatin has been shown to reduce LDL-C levels in patients with homozygous familial hypercholesterolaemia, despite the fact that these patients lack functional LDL receptors. This may reflect its capacity to inhibit cholesterol synthesis, which in turn reduces the rate of LDL-C production.[4]

2.1 Effect on Lipid Parameters Other Than Low-Density Lipoprotein Cholesterol

When evaluating the overall lipid-lowering efficacy of atorvastatin, it is important to consider its effect on other lipid parameters such as HDL-C and triglycerides. With regard to HDL-C levels, there appears to be a trend in some trials towards lesser increases in this parameter as the atorvastatin dosage is increased.[21] In the STELLAR trial, average increases in HDL-C levels were 4.8–5.7% with dosages of 10–20 mg/day, 4.4% with 40 mg/day and 2.1% with 80 mg/day.[19] However, this trend was not confirmed by intervention trials in which dos-

ages of 80 mg/day were given, as increases in HDL-C levels of 6–7% have been reported.[24-29]

With regard to triglycerides, although it is well known that the lowering effect of statins on these plasma lipids is essentially driven by their basal plasma levels (being larger in presence of hypertriglyceridaemia, and small or negligible in normotriglyceridaemia), it can be noted that atorvastatin produces a decrease in triglyceride levels of around 13–32%, which appears to be greater than that achieved with simvastatin and pravastatin,[30-32] and similar to that observed with rosuvastatin.[33] Reductions in triglyceride levels appear to be mainly due to decreased VLDL-C production as a consequence of apoB-100 synthesis inhibition (as apoB-100 is a necessary structural component of VLDL-C[34]). The increase in LDL receptors combined with a decreased availability of LDL-C to bind to them may increase binding of VLDL-C particles, thereby lowering triglyceride levels.[4]

2.2 Effect on Lipoprotein Composition

Another issue to take into account when evaluating the overall lipid-lowering efficacy of atorvastatin is its ability to positively modify lipoprotein composition. In a study comparing the effects of five different statins (atorvastatin, simvastatin, pravastatin, lovastatin and fluvastatin) on the lipid, lipoprotein and apolipoprotein profile of 86 patients with stable CHD,[35] atorvastatin proved to be the most effective agent in reducing LDL-C and triglyceride levels, and its effect on HDL-C and apoA-1 levels was comparable with that of the other statins. Interestingly, atorvastatin was capable of modifying the HDL subpopulation profile, increasing the average α-1 HDL fraction (an antiatherogenic particle, the level of which is very low in patients with a history of CHD), and decreasing the average α-3 fraction (a proatherogenic particle, the level of which is very high in CHD patients). The order of efficacy in increasing the α-1 HDL fraction was: atorvastatin, simvastatin, pravastatin, lovastatin and fluvastatin.[35]

The overall reduction in cholesterol and triglyceride levels induced by atorvastatin is associated with an improved LDL subfraction profile, with a shift towards the largest subfractions least involved in the atherogenic process. This effect has been noted in patients undergoing therapy with other statins (simvastatin and pravastatin) who had switched to atorvastatin.[36] In addition, atorvastatin has been shown to reduce the excessive sensitivity of LDL-C to oxidation, although this could relate more to the effect of the active hydroxy metabolites than to the parent drug.[37]

Thus, on the basis of current evidence, atorvastatin is one of the most effective statins for the treatment of lipid disorders. This can be concluded not only by considering its effects on LDL-C levels and its ability to meet recommended treatment guidelines for this parameter, but also taking into account its effect on levels of HDL-C and triglycerides, and its capacity to modify lipoprotein composition in a non-atherogenic manner.[38]

3. Is Lower Better? The Evidence with Atorvastatin

The issue as to whether it is better to focus on obtaining maximal reduction of LDL-C levels (the so-called 'lower is better' approach) in patients who are candidates for statin treatment or on cardiovascular outcomes has been debated. Trials undertaken with atorvastatin may be helpful in shedding light on this question.

A substudy of the PROVE-IT (PRavastatin Or atorVastatin Evaluation and Infection Therapy) study, in which patients with prior acute coronary syndromes who were treated with intensive atorvastatin therapy were divided into different groups depending on the specific LDL-C levels attained (>2.1–2.6 mmol/L [>80–100 mg/dL], >1.6–2.1 mmol/L [>60–80 mg/dL], >1.0-1.6 mmol/L [>40–60 mg/dL] and ≤1.0 mmol/L [≤40 mg/dL]), indicated that the lowest occurrence of cardiovascular events was in the groups with the lowest LDL-C levels (26.1%, 22.2%, 20.4% and 20.4%, respectively, for the various groups; $p_{trend} = 0.1$).[39] A multivariate analysis revealed that the cardiovascular event rates in groups attaining LDL-C levels between 1.0 and 1.6 mmol/L (40–60 mg/dL) or

≤1.0 mmol/L (≤40 mg/dL) were substantially lower than the reference group (>2.1–2.6 mmol/L [>80–100 mg/dL]) [hazard ratios of 0.67 and 0.61, respectively, for the >1.0–1.6 and ≤1.0 mmol/L groups].[39]

This finding reinforces a strategy outlined in the recent update to the NCEP clinical practice guidelines[40] aimed at achieving the lowest LDL-C levels possible, particularly in high-risk patients with CHD and other cerebro- and cardiovascular disease. While guidelines recommend reductions in LDL-C levels to <2.6 mmol/L (100 mg/dL) to be the overall goal of antihyperlipidaemic therapy in high-risk patients, the update offers the option of using drug therapy to achieve LDL-C levels <1.8 mmol/L (70 mg/dL) in patients who are at very high risk.[40] This hypothesis is in agreement with observations from recent trials. The TNT (Treating to New Targets)[41] and IDEAL (Incremental Decrease in Endpoints through Aggressive Lipid lowering)[25] trials have clearly demonstrated that treatment with atorvastatin 80 mg/day instead of atorvastatin 10 mg/day or simvastatin 20–40 mg/day leads to greater reductions of cardiac events in patients with stable CHD. These conclusions are not entirely surprising given that in a fairly healthy population without any symptoms of atherosclerosis, and in healthy neonates and native hunter-gatherer populations, cholesterol levels are within the range 1.3–1.8 mmol/L (50–70 mg/dL).[42] Data from extensive clinical trials and epidemiological studies indicate that there may be a linear or logarithmic association between the levels of LDL-C achieved and the reduction of cardiovascular risks. Consequently, additional reduction of the cardiovascular risk might be achievable with even lower LDL-C values than the ones observed in recent trials.[40,42]

The latter hypothesis is supported by data from a recent meta-analysis that evaluated four randomised controlled trials comparing intensive (high-dose) statin therapy with standard-dose statin therapy.[43] This analysis involved >27 000 patients with either stable CHD or acute coronary syndromes, and three of the four trials assessed atorvastatin therapy. The combined analysis revealed that standard-dose therapy produced a reduction in LDL-C levels of 22% (average value, 2.61 mmol/L [101 mg/dL]), whereas intensive therapy produced a reduction of 42% (average value, 1.94 mmol/L [75 mg/dL]) [figure 3]. This accounted for a final difference of 25.7% (2.61 vs 1.94 mmol/L) in LDL-C values between the two regimens.[43] In terms of effects on individual cardiovascular endpoints, the meta-analysis revealed a 16% odds reduction in the risk of coronary death or acute myocardial infarction with intensive versus standard-dose therapy (8.0% vs 9.4%; odds ratio 0.84; 95% CI 0.77, 0.91; $p < 0.00001$), as well as a 16% odds reduction in the risk of coronary death or any cardiovascular event (28.8% vs 32.3%; odds ratio 0.84; 95% CI 0.80, 0.89; $p < 0.0000001$) and an 18% reduction in the incidence of stroke (2.3% vs 2.8%; odds ratio 0.82; 95% CI 0.71, 0.96; $p = 0.012$). Analyses of non-cardiovascular mortality did not reveal any significant difference between the two regimens, while as far as total mortality is concerned, a nonsignificant positive trend favouring

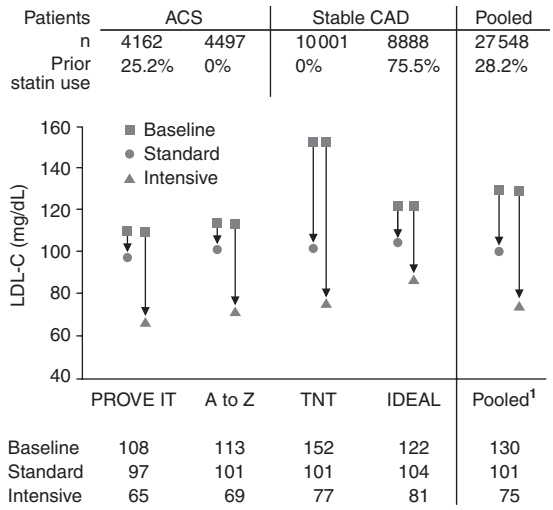

Fig. 3. Reduction of low-density lipoprotein cholesterol (LDL-C) values in a meta-analysis of three trials comparing high-dose with standard-dose statin therapy (reproduced from Cannon et al.,[43] with permission). **1** Values are estimated means. **A to Z** = Aggrastat to Zocor; **ACS** = acute coronary syndromes; **CAD** = coronary artery disease; **IDEAL** = Incremental Decrease in Endpoints through Aggressive Lipid lowering; **PROVE IT** = PRavastatin Or atorVastatin Evaluation and Infection Therapy; **TNT** = Treating to New Targets.

aggressive compared with standard treatment (risk reduction 6%; p = 0.2) was observed.[43]

Extrapolating these data, it can be inferred that for every 1 million people with chronic or acute coronary artery disease treated for 5 years, intensive statin therapy would prevent >35 000 cardiovascular events compared with standard-dose therapy. From this analysis, the number-needed-to-treat (NNT) to prevent a cardiovascular event corresponds to 29 patients treated for 2 years in the case of an acute coronary syndrome or 5 years in the case of stable CHD.[43] It should be emphasised that this benefit can be considered supplementary to that obtained with standard-dose statin therapy, which has also been shown to be highly effective in decreasing the incidence of cardiovascular events. When considered in the light of placebo-controlled trials of standard-dose statin therapy,[44] it is possible that the reduction in the rate of cardiovascular events with high-dose statins as compared with placebo could be as high as 40%.[43]

As indicated above, the NCEP guidelines[40] have established specific therapeutic goals in terms of LDL-C target levels depending on the individual patient's cardiovascular risk. These recommendations are based on the so-called 'risk curve' or the absolute risk for subsequent cardiovascular events over a range of LDL-C values,[45] which is a useful concept to consider when it comes to choosing the appropriate lipid-lowering therapy. In this regard, epidemiological studies have described a curvilinear association between the LDL-C levels and the cardiovascular event rate.[46,47] From data obtained in clinical trials of statins, including comparisons with placebo[48-50] and comparisons of different statin dosage regimens,[25,26,41,51] it can be concluded that studies employing a logarithmic model appear to give a clearer picture of the association between the LDL-C levels and cardiovascular risks than those employing a linear model. For persons with a very high cardiovascular risk, such as those with diabetes and CHD, a logarithmic model appears to fit slightly better than a simple linear model, whereas for persons with lower levels of risk (e.g. those with diabetes without cardiovascular disease [CVD], or neither CVD nor diabetes), logarithmic and simple linear models appear to perform equally well (figure 4).[45]

By applying logarithmic models, Robinson and Stone[45] have provided estimates of both the risk for cardiovascular events over approximately 5 years of treatment for various LDL-C levels and risk categories, and the NNT to prevent one cardiovascular event for each additional 0.8 mmol/L (30 mg/dL) reduction in LDL-C [table IV]. From these data, it would be reasonable to assert the following:

- although every LDL-C reduction of the order of 0.8 mmol/L (30 mg/dL) decreases the 5-year risk of cardiovascular events by 28–33% in patients with CHD and diabetes, NNT values for LDL-C reductions of this magnitude show a >10-fold variation between the highest and lowest CVD risk populations;
- after 5 years of treatment, patients with CHD and diabetes are faced with a significant residual CVD risk despite LDL-C levels of 1.8 mmol/L (14%) or <1.0 mmol/L (10%); and
- despite low LDL-C levels (1.8 mmol/L [70 mg/dL]), the residual 5-year cardiovascular risk is still significantly higher for CHD patients without diabetes, and is similar to that in patients with

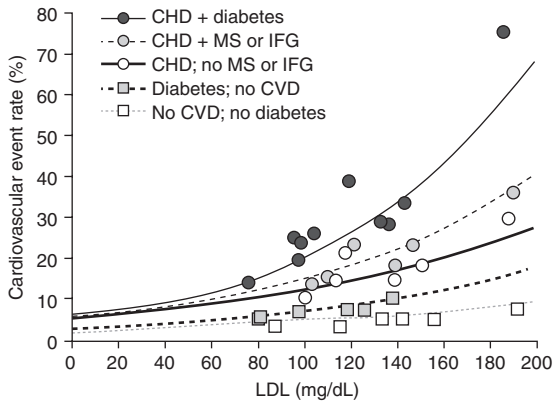

Fig. 4. Relation between low-density lipoprotein (LDL) cholesterol levels and the risk for cardiovascular events (nonfatal myocardial infarction, coronary heart disease [CHD] death and stroke) based on data from placebo-controlled trials of statins of approximately 5 years in duration (reproduced from Robinson and Stone,[45] with permission). **CVD** = cardiovascular disease; **IFG** = impaired fasting glucose; **MS** = metabolic syndrome.

Table IV. Estimates (from logarithmic models) of the risk for nonfatal myocardial infarction, coronary heart disease (CHD) death and stroke events over approximately 5 years (%) for various low-density lipoprotein-cholesterol (LDL-C) levels and cardiovascular disease (CVD) risk categories, and numbers-needed-to-treat (NNT) to prevent one event for each additional 0.8 mmol/L (30 mg/dL) reduction in LDL-C levels (reproduced from Robinson and Stone,[45] with permission)

LDL-C (mmol/L)	CVD risk category									
	all CHD		CHD + diabetes		CHD + MS or IFG		CHD; no MS or IFG		diabetes; no CVD		no CVD; no diabetes	
	5-year risk (%)		5-year risk (%)	NNT	5-year risk (%)	NNT	5-year risk (%)	NNT	5-year risk (%)	NNT	5-year risk (%)	NNT
4.9 (190 mg/dL)	27		62		36		27		16		9	
4.1 (160 mg/dL)	21		43	5	27	11	21	17	12	24	7	48
3.4 (130 mg/dL)	16		30	8	20	14	16	22	9	32	5	67
2.6 (100 mg/dL)	12		21	11	15	20	13	29	7	43	4	83
1.8 (70 mg/dL)	10		14	16	11	26	10	36	5	59	3	100
1.0 (40 mg/dL)	7		10	23	8	36	8	45	4	77	2	143
0	5		6		6		6		3		2	

IFG = impaired fasting glucose; **MS** = metabolic syndrome.

CHD plus metabolic syndrome or altered glucose tolerance (10% vs 11%, respectively).

These data confirm the importance of using an aggressive lipid-lowering strategy in patients with the highest cardiovascular risk and provide the rationale for the NCEP-recommended therapeutic goals for LDL-C level reduction depending on the cardiovascular risk category.[40]

Another factor that influences the success of lipid-lowering therapy is how appropriately it is administered. Unfortunately, there is a significant gap between international dyslipidaemia management recommendations and current clinical practice.[52] Studies conducted in the US and Sweden have indicated that dyslipidaemia is still underdiagnosed and, among patients in whom it is detected, only a relatively small proportion undergo treatment and/or achieve recommended therapeutic goals.[53-55] This serious limitation is also common in Italy, as evidenced by observational data showing that only 20% of the diabetic population in specialised diabetic clinics receive statin therapy, and by a study of general healthcare indicating that a high percentage of high-risk patients (10-year cardiovascular risk >20%) are currently not treated with statins.[56,57]

4. Conclusions

In summary, the available clinical evidence has emphasised the effectiveness of statin therapy in achieving a substantial LDL-C reduction. It also underlines the importance of continuing such therapy in patients at increased risk of CHD and other major cardiovascular events, particularly in view of the clinical and social impact that such an outcome could have.[44]

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