Therapeutic Controversies

Lack of Therapeutic Interchangeability of HMG-CoA Reductase Inhibitors

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OBJECTIVE: To review relevant literature and provide an opinion on the class effect of hydroxymethylglutaryl coenzyme A reductase inhibitors (statins).

DATA SOURCES: Primary and review articles were identified by MEDLINE search (1990–July 2002).

STUDY SELECTION AND DATA EXTRACTION: Editorials, studies, and review articles related to the class effect or therapeutic interchangeability of statins were reviewed. Also included was information that is relevant to this topic.

DATA SYNTHESIS: Although statins share common main actions, they may have clinically important differences in terms of efficacy and safety. At fixed or allowable dosages, rosuvastatin, atorvastatin, and simvastatin produced greater low-density lipoprotein cholesterol–lowering effects compared with other statins. Some statins have shown reduction in either cardiovascular and/or total mortality. Statins also differ in their structure, pharmacokinetics, potency, and rate of metabolism, any or all of which may have clinical significance. Although inconclusive, subtle differences in nonlipid effects of some statins may have contributed to positive benefits observed in clinical studies. As a result of drug-related deaths, cerivastatin was withdrawn voluntarily from the market, which may raise the question whether there is therapeutic interchangeability (due to class effect) among statins.

CONCLUSIONS: Despite the competition for market share and strategies attempting to identify differences in therapeutic value, few head-to-head comparisons between statins have been performed. The limited, available data suggest that statins are not therapeutically interchangeable.

KEY WORDS: hydroxymethylglutaryl coenzyme A reductase inhibitors, therapeutic interchange.

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See also page 1961.

After the safety and efficacy of a drug in a new class have been established, it is not unusual to see the introduction of additional drug members of the same class. These newer agents may or may not offer advantages such as higher tissue selectivity/affinity and penetration, different duration of action, or lower incidence of adverse effects. This approach to new drug introduction has many advantages and is useful for teaching, drug development, marketing, and reducing cost.[1,2]

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Currently, >80% of hospitals in the US use programs that permit the interchange of therapeutically equivalent, but chemically unique drugs, according to established policies and procedures within an evidence-based formulary.[3] However, to assume that all agents within a drug class are therapeutically equivalent and so can be used interchangeably may not be warranted. The critical question for practicing clinicians is: "Are all drugs within a class therapeutically interchangeable since they are deemed to exert class effect?"[1] In many instances, there may not be enough clinical evidence available to provide a definitive answer. In practice, the answer may depend on how convinced clinicians and hospital/institution policy makers are that all drugs in a class share the main clinical action often referred to as the class effect.

An evaluation of the literature reveals that there is no formal definition of the term class effect,[1,2,4] and no accepted clinical, scientific, or regulatory criteria for establishing a class effect.[2,5] Criteria for drug class are neither uniform nor absolute. They are usually divided into categories to suit dissimilar purpose, which may change over time. The 2 key criteria for drug class membership are: variables used for categorization (e.g., chemical structure, modes of action, pharmacologic effects, therapeutic applications) and the degree of similarity. These criteria define the homogeneity of the drug class, and the more homogeneous a class is, the more interchangeable the drugs of that class are considered to be. Presumably, this would confer similar efficacy and clinical outcomes.[4] However, Food and Drug Administration (FDA) approval only requires proven efficacy shown in clinical trials; approval does not require direct comparison to existing agents and evaluation to determine whether either agent is more effective. Thus, these definitions have also facilitated the development of newer drugs without track records that would allow them to be marketed as interchangeable alternatives to those with proven outcomes. The lack of clear guidance allows for comparability of agents as for proof of efficacy and may have unfavorable consequences for the practice of medicine.[1-3,5]

In cardiovascular practice, particular attention is given to hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins). At present, 5 statins are available in the US: atorvastatin, fluvastatin, pravastatin, simvastatin, and lovastatin. Rosuvastatin is an investigational agent, which is planned to be released in the near future. In August 2001, cerivastatin, the newest statin at the time, was voluntarily withdrawn from the US market because of reports of potentially fatal rhabdomyolysis.[6] The fact that this drug alone was removed suggests that all statins may not be interchangeable. The primary objective of most statin therapeutic interchange programs is cost reduction[1-5]; other important aspects include safety, related or unrelated drug actions (beneficial or harmful), and effects on lipid lowering, atherosclerosis, and cardiovascular events. Whether or not these variables translate into clinically significant differences remains unresolved and controversial.

The purpose of this article is to review the class effect concept as it applies to statins. The data presented differentiate the above-stated variables and make the argument that statins do not exhibit a class effect.

Chemical Structures

Members of a drug class are often divided into subclasses based on chemical structures. The chemical structure of an agent may possess unique properties that are not shared by members of other subclasses, and these properties may exert different clinical effects. Currently, available statins are classified into 2 subclasses: naturally or fungi-derived first-generation statins (lovastatin, pravastatin, simvastatin), and synthetically or hepatenoic acid–derived second-generation statins (atorvastatin, fluvastatin). Rosuvastatin is considered a new second-generation statin that contains a sulfur moiety. The structural differences between first- and second-generation statins are apparent by the binding domain[7-11] (Figure 1).[7] Both generations have an equal number of binding interactions with the HMG-CoA reductase molecule, and the second-generation agents have an additional polar interaction through the fluorophenyl group. Atorvastatin and rosuvastatin have additional hydrogen bonding; rosuvastatin also has increased binding interaction due to the methane sulfonamide group.[7-11]

It is likely that these subtle structural differences have an impact on the modes of action (i.e., ability to interact with the HMG-CoA reductase molecule and inhibition of the enzyme) and human physiology. This may be the case with other classes of drugs. For example, small structural differences in testosterone, estrogen, and progesterone molecules account for some of the most important differences in human physiology.[12] It is plausible that the same degree of structural difference may be responsible for enhancing or diminishing the overall clinical effects observed with statins; however, it is unsubstantiated at this time.

Modes of Action

Drugs exhibiting a class effect should have a single, common mode of action. Statins competitively inhibit HMG-CoA reductase, the enzyme that catalyzes the rate-limiting step in cholesterol biosynthesis. The resultant reduction in hepatocyte cholesterol concentrations triggers increased expression of hepatic low-density lipoprotein (LDL) receptors that clear LDL-cholesterol (LDL-C) and LDL precursors from the circulation. By the same mechanism, statins also inhibit hepatic synthesis of apolipoprotein B-100 and decrease the synthesis and secretion of triglyceride-rich lipoproteins (very-low density lipoprotein [VLDL] and intermediate-density lipoprotein [IDL]).[13-15] The degree of this commonly shared mechanism in affecting lipoprotein concentrations depends on the potency (mg/mg basis) of the conversion and specific inhibition on HMG-CoA reductase (mevalonic acid concentrations as a marker) thereby, cholesterol biosynthesis in hepatic tissues by different statins at fixed or allowable dosages (Table 1).[9,12,13,16]

It is possible that the greater reduction in hepatic production and secretion of lipoproteins resulting from inhibition of HMG-CoA reductase/cholesterol biosynthesis is a function of the more potent statins (simvastatin, atorvastatin, rosuva-statin). It can be inferred that the more potent reduction in LDL-C, the more significant reduction in VLDL and IDL, commonly referred to non–high-density lipoprotein cholesterol (HDL-C) (total cholesterol – HDL-C).[11] The difference in chemical structure (i.e., additional binding interactions) may offer the basis for this observation. Both atorvastatin and simvastatin have FDA-approved use for lowering LDL-C as an adjunct to LDL-C aphaeresis (filtration of LDL-C) in patients with homozygous familial hypercholesterolemia (HFH) who have no functional LDL receptors.[17,18] Although studies[19] with other statins in HFH are limited, they show less than desirable effects for this adjunct indication.

Pharmacokinetic Effects

Structural differences may also account for differences in pharmacokinetic and pharmacologic properties. Some pharmacokinetic differences may affect the choice of 1 statin over another in a given clinical situation (Table 1).[9,12,13,16] For example, while all statins are excreted through urine and feces, the relative proportion excreted by each route differs.[12-15] In patients with severe renal impairment, reduced doses of all statins except atorvastatin or fluvastatin should be considered.[13] The absorption varies from 30% with lovastatin to 98% with fluvastatin and bioavailability of the statins varies from <5% with simvastatin to 24% with fluvastatin.[13] The respective elimination half-lives of atorvastatin and rosuvastatin are approximately 14 and 20 hours, respectively, considerably longer than that of other statins (≤4 h).[8,9,17] As a result, these statins have equal LDL-C–lowering efficacy whether administered in the morning or evening, while other statins are more effective when administered in the evening.[8,9,13,17] All statins, except pravastatin, are removed extensively through first-pass hepatic metabolism by the cytochrome P450 enzyme system (see below).

The overriding differences, however, among the statins in pharmacokinetics and pharmacologic effects concern their relative lipophilicity and hydrophilicity.[12] Simvastatin, lovastatin, and atorvastatin are relatively lipophilic, while fluvastatin, pravastatin, and rosuvastatin are essentially hydrophilic. Clinically, these differences have a major impact on tissue affinity/selectivity and penetration (e.g., hepatic, blood–brain barrier), and the potential for drug interactions (see below). For example, compared with lipophilic statins, hydrophilic statins are less likely to cross the blood–brain barrier to cause insomnia (overall incidence <3%).[13,20] This fact may guide the clinician to select a hydrophilic statin for a patient with insomnia.

Drug Interactions

Pharmacokinetic differences among the statins also have ramifications on clinically significant drug–food interactions. Although statins are predominantly metabolized by the hepatic cytochrome P450 system, they are metabolized by different isoenzymes within the system (Table 1).[8,9,12-15] This metabolic difference has major clinical implications regarding drug interactions. Atorvastatin, lova-statin, and simvastatin are predominantly metabolized by the CYP3A4 isoenzyme. Fluvastatin is metabolized by the CYP2C9 isoenzyme and rosuvastatin is metabolized by CYP2C9 and 2C19.[8,9] Pravastatin is primarily eliminated by a renal mechanism (sulfation). Statins metabolized by CYP3A4 have the potential to interact with other drugs, such as erythromycin, cyclosporine, diltiazem, antiretroviral agents, and gemfibrozil, which are metabolized by the same pathway.[12-15] These interactions can cause the circulating concentrations of the statins to increase, which may result in serious adverse effects such as myopathy or, in extreme cases,

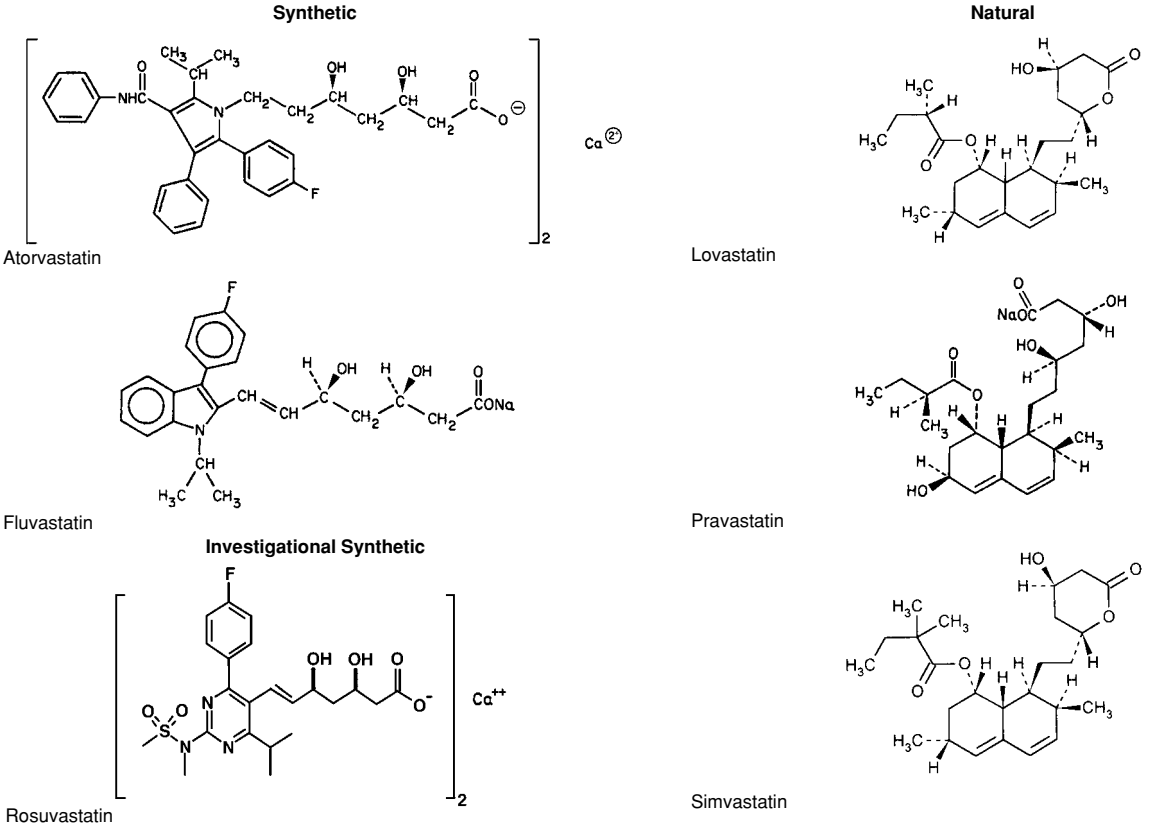

Figure 1. Chemical structures of the natural and synthetic-derived available statins, including the investigational agent rosuvastatin.[7]

rhabdomyolysis.[6,12] Because statins are prescribed on a long-term basis, patients can receive 1 of these potentially interacting drugs during the course of therapy.

The interaction of statins with fibrates (e.g., gemfibrozil) is particularly important, since patients with mixed dyslipidemia are often treated with multiple lipid-lowering agents. The mechanism for this drug interaction is unclear. The reason for removal of cerivastatin from the market was myopathy-related deaths occurring in patients on high doses (0.8 mg) of cerivastatin (metabolized by CYP3A4, 2C8) either alone or in combination with gemfibrozil, an inhibitor of CYP3A4.[6] This suggests that cerivastatin had a greater propensity to cause myopathy than other statins. Prior to drug withdrawal, the package labeling[21] stated that combined use of cerivastatin and gemfibrozil was contraindicated due to a risk of rhabdomyolysis.

A warning label is currently used for simvastatin and atorvastatin.[17,18] A dosage limit of simvastatin (10 mg/d) has recently been added to its labeling if combined with fibrates. Additionally, it is recommended to reduce the dose of simvastatin to 20 mg/d when combined with amiodarone and verapamil to decrease the potential for myopathy.[18] Regarding solid food interactions, all current statins, except lovastatin, may be taken without regard to meals.[13] Solid foods may increase the bioavailability of lovastatin by as much as 50%.[13]

Pharmacologic Efficacy

LIPID-LOWERING EFFECT

Statins are highly effective in reducing LDL-C (18–55%) and modestly effective in increasing HDL-C (5–15%). Triglyceride lowering (7–30%) is directly proportional to the baseline triglyceride concentration and to the LDL-C–lowering potency of the statin.[22] In patients without hypercholesterolemia, statins reduce total cholesterol and LDL-C by an additional 5% and 7%, respectively, with each doubling of the dose, and increase HDL-C by 7% across all doses. This is often referred to as the "rule of 5 and rule of 7."[23] These lipid-lowering effects of statins are widely accepted in clinical practice, but there is some question as to what is meant by equipotent efficacy (i.e., within the class).

Although all statins lower LDL-C concentrations, they do so in varying degrees. The magnitude of the LDL-C decrease varies according to several factors: the specific statin, the dosage form, increases in the allowable dosage, and whether hypertriglyceridemia coexists. While the rule of 5 and rule of 7 is generally applicable, exceptions occur (Table 2).[24-27] Higher doses of selected statins should be considered; however, more potent statins such as atorvastatin or simvastatin (or rosuvastatin when available) at moderate doses may represent the best choices for initial therapy in conjunction with therapeutic lifestyle changes.[22] Alternatively, consideration should be given to changing dosing frequency from once to twice daily (lovastatin or fluvastatin 40 mg twice daily) or using extended-release fluvastatin 80 mg/d where the amount of LDL-C lowering will increase by 10%.[28]

Accordingly, the question of appropriate dose of statins and additional clinical benefits of further LDL-C lowering are far from being settled.[7,15] The results from the PPP (Pravastatin Pooling Project)[29] and previous statin trials[30,31] support the broad use of pravastatin at appropriate doses (40 mg/d) for secondary prevention of coronary heart disease (CHD). A recent finding from the HPS (Heart Protection Study),[32] which included 20 536 subjects, showed that simvastatin 40 mg/d provided clinical benefits when used as primary and secondary prevention. This finding further supports the appropriate dose theory.[32] Several ongoing clinical and surrogate endpoint trials[7] are intended to provide this information regarding statins and optimal target reduction of LDL-C. There are also questions about the recommended or optimal dose of statins (low vs. high) associated with the best clinical outcomes. It is possible that dosing of statins cannot be determined only from LDL-C reduction. Several ongoing trials, including TNT (Treating to New Targets) (atorvastatin 10 vs. 80 mg) and SEARCH (Study to Evaluate Additional Reductions of Cholesterol and Homocysteine; simvastatin 20 vs. 80 mg), promise to answer this question. Further, the extent of LDL-C lower-

Table 1. Pharmacokinetic and Pharmacologic Differences Among Current and Investigational Statins[9,12,13,16]

Statin	Absorption (%)	Bioavailability (%)	Half-Life (h)	Urine Excretion (%)	Hydrophilic/ Lipophilic[a]	Metabolism	Potency on HMG-CoA Reductase IC_{50} (nM)	Potency on Cholesterol Synthesis IC_{50} (nM)
Atorvastatin	rapid	12	14	<2	lipophilic, 3	CYP3A4	8.2	1.16
Fluvastatin	98	24	<1	5	hydrophilic, 2	CYP2C9	27.6	3.78
Lovastatin	30	<5	3–4	10	lipophilic, NA	CYP3A4	NA	NA
Pravastatin	35	17	1.8	20	hydrophilic, 5	sulfation	44.1	6.93
Rosuvastatin	NA	NA	20	10	hydrophilic, 4	CYP2C9 CYP2C19	5.4	0.16
Simvastatin	60–85	<5	3	13	lipophilic, 1	CYP3A4	11.2	3.54

HMG-CoA = hydroxymethylglutaryl coenzyme A; IC_{50} = 50% inhibitory concentration; NA = not available.
[a]Rank order of relative lipophilicity (log D at pH 7.4).

ing may also be affected by factors such as interindividual or genetic variability (e.g., apo E-4) when extrinsic influences such as diet and compliance are minimized.[33,34] These factors may be largely independent of the statin and dose used.[33]

Since low HDL-C (<40 mg/dL) is now regarded as a part of overall risk correction,[22] some consideration should be given to the HDL-C–elevating effects of different statins. There appears to be a flat dose–response curve for statins and associated increases in HDL-C, such that low- or high-dose statins affect HDL-C in a similar fashion (Table 2). Atorvastatin, fluvastatin, pravastatin, and simvastatin have an FDA-labeled use for increasing HDL-C concentrations,[17,18,35,36] and clinical trials[27,41-43] have shown a similar or slightly greater increase in HDL-C concentrations with rosuvastatin.[27,37-40] Simvastatin has consistently demonstrated the best results in elevating HDL-C concentrations. Some data[24,41-43] suggest that HDL-C–increasing effects may be attenuated or even reversed with some higher doses of statins (notably atorvastatin). Studies indicate considerable variability among statins in their effect on HDL-C, the clinical significance of which remains unclear. This makes it likely that differences exist in the metabolic effects of different statins, although those differences remain to be fully established. Lowering of triglyceride concentrations using statins is also of uncertain clinical importance. While minor differences in efficacy exist, none of the approved statins has a documented advantage in clinical outcomes.

Table 2. Percentage Change in Plasma Concentration of Cholesterol and Triglycerides with Approved Dosages of Statins in Patients with Hypercholesterolemia

Statin	Dose (mg)	TG (% ↓)	HDL-C (% ↑)	LDL-C (% ↓)
Atorvastatin[24]	10	13	5.5	38
	20	20	5.1	46
	40	32	4.8	51
	80	25	0.1 reduction	54
Fluvastatin[24,25]	20	5	0.9	17
	40	13	3.0 reduction	23
	80[a]	35	12	36
Lovastatin[24]	20	12	7.3	29
	40	2	4.6	32
	80[b]	13	8.0	48
Pravastatin[24]	10	3 increase	9.9	19
	20	15	3.0	24
	40	10	6.2	34
Rosuvastatin[27]	5	35	14	41
	10	10	14	48
	20	23	10	55
	40	28	10	62
	80	23	13	65
Simvastatin[24,26]	10	12	6.8	28
	20	17	5.2	35
	40	15	9.6	41
	80	36	10.0	46

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.
[a]Extended-release formulation (36%); 40 mg twice daily (32%).
[b]40 mg twice daily.

NONLIPID EFFECTS

The foregoing information suggests that if investigators focus on only 1 action (LDL-C lowering), other important actions of statins may go unnoticed. Statins have biological effects independent of lipid lowering, including antiproliferative effects on smooth muscle cells, restoration of endothelial activity, antioxidant effects, antithrombotic effects, and antiinflammatory effects, all of which have been identified in experimental settings. These properties, collectively known as nonlipid or pleiotropic effects, may differ from 1 statin to another,[4,13,15,44-48] which may be related to structural and pharmacokinetic differences. Table 3[49-94] depicts the different nonlipid effects of currently available statins shown in primary literature. Some statins have demonstrated other unique properties not yet shown by other agents in the class. For example, atorvastatin has been shown to improve heart rate variability[95] and aortic elasticity (unpublished observation), which may contribute to reduced clinical outcomes in patients with CHD. Pravastatin may modify (or down-regulate) the expression of the CD40 ligand on activated platelets during prothrombotic and proinflammatory response, which may initiate and increase the progression of atherosclerosis.[96]

Meta-analyses[97,98] of lipid-lowering drugs suggest that the risk of myocardial infarction for patients treated with statins is significantly lower than that for those treated with other drugs despite comparable reductions in serum cholesterol in both groups. These findings suggest that statins may have beneficial effects beyond cholesterol lowering. Angiographic trials provide evidence that differences among statins in this regard may exist. Findings from several long-term, randomized, placebo-controlled angiographic trials[13-15,99] have supported the preventive effects of all statins except atorvastatin and rosuvastatin in both decreasing lipid concentrations and the progression/regression of atherosclerotic lesions, contributing to a reduction in cardiovascular events. Ongoing head-to-head studies used electron beam–computed tomography (PROVE-IT [Pravastatin or Atorvastatin Evaluation and Infection Therapy], pravastatin vs. atorvastatin; BELLES [Beyond Endorsed Lipid Levels Evaluation Study], pravastatin vs. atorvastatin) or improved intravascular ultrasound (ASAP [Atorvastatin versus Simvastatin on Atherosclerosis Progression], atorvastatin vs. simvastatin) to determine whether statins improve the anatomic features of coronary disease.[7] The positive findings with atorvastatin in acute coronary syndrome also provide evidence that nonlipid effects play a major role in reducing recurrent ischemic events as early as 16 weeks, suggesting a prominent role in endothelial activity when initiated during an acute episode.[100] Fluvastatin in the setting of acute myocardial infarction has also shown[101] a beneficial trend. Pravastatin also provides cardiovascular benefit when combined early with thrombolytic therapy[102] or percutaneous coronary angioplasty[103] at 6 and 24 months, respectively. There are ongoing trials with simvastatin and atorvastatin that will hopefully delineate the degree of any benefit from early statin initiation in

acute MI and attempt to explore the nonlipid mechanisms that may modulate the pathophysiology of acute MI.[104]

In evaluating noncoronary effects of statins, fungi-derived statins (lovastatin, pravastatin, simvastatin)[105] and 1 synthetic-derived statin (atorvastatin)[106] have demonstrated[13] the ability to prevent stroke and reduce development of peripheral vascular disease. This raises the question of whether these agents can reduce ischemic stroke independent of lowering cholesterol concentrations. Subanalysis showed that simvastatin reduced the risk of stroke or transient ischemic attack (TIA) by 28%[107] and also reduced the incidence of lower extremity atherosclerosis.[108] The HPS trial[32] showed a reduction of stroke by 25% of all types in a wide range of high-risk patients. Pravastatin reduced all-cause stroke and stroke or TIA by 32% and 27%, respectively.[109] In a large randomized trial,[106] atorvastatin reduced stroke by 57% compared with "usual" care. Large cohort studies[13] on various statins have shown effects on essential hypertension, colon cancer, osteoporotic fracture, ventricular arrhythmias, immune response, and dementia. The clinical importance of nonlipid effects on these therapeutic targets is still being delineated. Although all statins act on HMG-CoA reductase, they may have different nonlipid effects on the atherothrombotic process that may influence their clinical efficacy.

Effects on Cardiovascular Events

The consequences of drug selection within a class for chronic therapy are unclear, because the evidence of efficacy or questions of safety may not be apparent for many years.[2] The optimum source of comparative information on preventive effects for head-to-head comparisons within a class would be large randomized trials of efficacy (at every dose and formulation), safety, and cost-effectiveness.[1-4,110,111] As previously stated, the FDA and most other regulatory agencies,[2,5] however, do not require such head-to-head comparisons. Thus, drug companies commonly invoke the class-effect concept to compensate for lack of data for a specific agent within a class. Any study able to demonstrate a clinically significant difference between statins would need to be very large and also demonstrate mortality differences. Some groups claim there is a class effect for the occurrence of cardiovascular disease based on the cumulative data from landmark statin trials (Table 4).[4,30-32,108,112,113] This clinical evidence is applicable to 3 fungi-derived statins (pravastatin, lovastatin, simvastatin). Both pravastatin and simvastatin have been shown to reduce overall mortality and deaths due to coronary disease,[30,31,111,112] while lovastatin has been shown to reduce only coronary events.[113] Additionally, simvastatin reduced all-cause and cardiovascular deaths in patients with average cholesterol concentrations and CHD (with or without an antioxidant combination of vitamins E, C, and β-carotene).[32] This is a case of evidence supporting the preferential use of a specific drug in clinical practice.

The issue of cardiovascular outcomes (mainly mortality) remains unresolved for other statins. Atorvastatin and fluvastatin have been evaluated in relatively short-term studies with inconclusive results. Aggressive atorvastatin therapy (80 mg/d) in 164 patients reduced ischemic events when compared with those undergoing angioplasty (n = 177), but showed no overall statistical significance after interim analysis adjustment of 341 patients.[114] The use of atorvastatin in acute coronary syndrome resulted in reduced combined primary endpoints and the secondary endpoint of recurrent ischemic events requiring hospitalization.[100] However, a recent secondary prevention trial, the GREACE (GREek Atorvastatin and Coronary-heart-disease Evaluation)[106] showed that, after 3 years, atorvastatin reduced total mortality by 43% and coronary mortality by 47% compared with "usual" care. But a direct comparison with the landmark statin trials (4S [Scandinavian Simvastatin Survival Study], CARE [Cholesterol and Recurrent Events], LIPID [Long-term Intervention with Pravastatin in Ischemic Disease]) cannot be made, since the latter trials

Table 3. Comparison of Available Statins on Major Nonlipid Effects that Modify Atherosclerotic Processes

Potential Mechanism	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Simvastatin
Antiatherosclerotic					
smooth muscle cell proliferation	↓[49]	↓[49]	↓[49]	■[49]/↓[50]	↓[49,50]
endothelial dilation	↑[51,52]	↑[56,57]	↑[53,54]	↑[58,59]	↑[55]
LDL oxidation	↓[60,61]	↓[61]	↓[62]	↓[64]	↓[63]
Antithrombotic					
platelet aggregation and deposition	↓[65]	NA	■[66]/↓[67]/↑[68]	■[69,71]/↓[68]	■[69]/↓[70]
fibrinogen	■[72]/↓[73]/↑[74,75]	↓[72]	■[66]/↓[67]/↑[68]	■[77]/↓[75,76]	■[76,77]/↓[75]
fibrinolysis					
PAI-1	↑[78]	↑[80]	↑[78]	↓[81]	↑[79]
lipoprotein (a)	NA	■[80]	↓[82]	↑[84]	↑[83]
Antiinflammatory					
monocyte–endothelial cell adhesion	↓[85]	↓[86]	↓[86]	NA	↓[86]
cytokines[a]	↓[87,88]	↓[88,90]	↓[89]	↓[89,91,92]	↓[89]
high-sensitivity C-RP	■[75]/↓[93]	NA	NA	↓[93,94]	■[75]/↓[93]

C-RP = C-reactive protein; LDL = low-density lipoprotein; NA = not available; PAI-1 = plasminogen activation inhibitor 1; ■ = no/minimal effect; ↓ = decrease/inhibition; ↑ = increase/enhance.
[a]For example, tumor necrosis factor-α, interleukin-6 and -8.

compared a statin with a placebo for ≥5 years in a double-blind fashion, used a different study objective and older cholesterol treatment guidelines, and had interpopulation differences in CHD mortality rates. While the results are positive, the GREACE trial may be criticized as being far from definitive. Data from a small observation, the FLORIDA (FLuvastatin On RIsk Diminishing After acute myocardial infarction) trial,[101] provided no overall cardiovascular benefit but a beneficial trend after 1 year in patients with severe ischemia at baseline. Additionally, the LIPS (Lescol Intervention Prevention Study)[115] showed that patients with average cholesterol concentrations treated with fluvastatin and undergoing their first percutaneous coronary interventions had significant reduction of major coronary events.

Despite the lack of overwhelming long-term clinical evidence with both atorvastatin and fluvastatin, some clinicians use them to lower LDL-C concentrations with the expectation that their effect on this surrogate marker will translate into a reduction in cardiovascular events.[12,13] To this testimony, the most commonly prescribed statin in the US is atorvastatin.[116] The results of the GREACE study[106] would lead clinicians to expect the prescribing of atorvastatin to be even higher. Nevertheless, there are major limitations associated with reliance on surrogate efficacy.[117-119] These drugs have >1 effect when introduced into complex biological systems, and effectiveness of therapy should not be confused with mechanism of action (i.e., LDL-C lowering); therefore, surrogate markers may be poor predictors of clinical efficacy.[1,2] Also, statins may have multiple mechanisms of action (see Nonlipid Effects). Finally, a member of a drug class can claim interchangeability for a specific indication or use only after specific testing,[1,2] no matter how strong the pathophysiologic rationale or indirect evidence.[4] It is inappropriate to extrapolate cardiovascular outcomes shown in randomized trials of 1 statin in a class to statin that has not been studied. Findings from ongoing clinical-endpoint, head-to-head statin trials will soon be available to provide answers about the variations among statins and clinical outcomes. IDEAL (Incremental Decrease in Endpoints through Aggressive Lipid Lowering) (atorvastatin 80 mg vs. simvastatin 20–40 mg) will be evaluating the primary endpoint of coronary artery disease death or nonfatal myocardial infarction.[7]

Safety Profile

ADVERSE EFFECTS

Small short-term studies designed to observe the effects of statins on lipoproteins provide insufficient data on drug safety. There are no surrogates for drug safety. Accordingly, the FDA[120,121] has issued letters of warning to the manufacturers of atorvastatin and fluvastatin regarding false claims about existing health benefits. To ensure safety, potential molecules with harmful effects are eliminated during drug development.[2] Several individual drugs of established classes have been found to cause major harm, leading to postmarketing drug withdrawal (troglitazone, mibefradil). Although there appears to be no apparent differences in safety with statins,[4] the withdrawal of cerivastatin has caused some

Table 4. Summary of Landmark Statin Clinical Trials

	Secondary Prevention		Secondary/ Primary Prevention	Secondary Prevention	Primary Prevention	
Trial (duration)	CARE (5 y)[30] (n = 4139)	LIPID (6.1 y)[31] (n = 9014)	HPS (5.3 y)[32] (n = 20 536)	4S (5 y)[108] (n = 4444)	WOSCOPS (4.9 y)[112] (n = 6595)	AFCAPS/ TexCAPS (5.2 y)[113] (n = 6605)
Statin/dose (mg/d)	pravastatin 40	pravastatin 40	simvastatin 40	simvastatin 20–40	pravastatin 40	lovastatin 20–40
Level of risk	average (MI)	average (MI or angina)	wide range of high or CAD (MI, angina)	high (MI or angina)	high	average
Baseline TC (mg/dL)	209	155–270	>135	259	272	221
LDL-C reduction from baseline (%)	28	25	22–40%	35	26	25
Results (risk reduction)	CHD death or nonfatal MI (24%), fatal/nonfatal MI (25%), fatal/ nonfatal stroke (31%)	total mortality (22%), CHD death (24%), CHD death or nonfatal MI (23%), fatal/ nonfatal MI (29%), fatal/nonfatal stroke (20%)	total mortality (12%); MI, stroke, vascular death (17%); coronary death or nonfatal MI (27%); stroke (25%)	total mortality (30%), CHD mortality (42%), CHD death or nonfatal MI (34%)	nonfatal MI (31%), CHD death or nonfatal MI (33%)	fatal/nonfatal MI, unstable angina, sudden cardiac death (37%); fatal/ nonfatal MI (40%); unstable new-onset angina (32%); fatal/nonfatal CV event (25%)

AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; CARE = Cholesterol and Recurrent Events; CHD = coronary heart disease; CV = cardiovascular; HPS = Heart Protection Study; LDL-C = low-density lipoprotein-cholesterol; LIPID = Long-term Intervention with Pravastatin in Ischemic Disease; MI = myocardial infarction; 4S = Scandinavian Simvastatin Survival Study Group; TC = total cholesterol; WOSCOPS = West of Scotland Coronary Prevention Study.

concern regarding whether there is a class effect to myopathy-related events (i.e., rhabdomyolysis) (see also Drug Interactions). Cerivastatin is at least 10 times more likely than other statins to cause fatal rhabdomyolysis.[117] Small short-term studies with cerivastatin provided insufficient data on drug safety. Current documentation with fluvastatin or rosuvastatin is weak or nonexistent. In a 3-year follow-up,[106] atorvastatin was well tolerated, with no reports of myopathy. However, several ongoing trials will provide important safety data with these statins. Comparative long-term safety of drugs can be determined accurately only in large, long-term trials or well-designed observational studies with the necessary statistical power.

The risk of liver toxicity with statins must also be considered. The incidence of liver transaminase concentrations >3 times the upper limit of normal is approximately 1%, regardless of which statin and dose is used. However, package labeling varies for each statin for monitoring liver function tests.[13,17-19,35,36]

Summary

Based on this review of limited data regarding statins, the following can be stated:

1. There are structural differences among statins.
2. All statins have similar modes of action; however, there are differences in relative potency for HMG-CoA reductase and cholesterol biosynthesis.
3. There are differences among statins in their pharmacokinetic properties including relative lipophilicity, half-life, and potential drug–food interactions due to their dissimilar chemical structures. The recent revision on drug interactions in simvastatin labeling[18] has heightened awareness of potential drug-induced myopathy.
4. At equipotent doses, all statins have similar LDL-C–lowering effects; however, some statins exhibit significant differences at fixed or allowable doses (rosuvastatin > atorvastatin > simvastatin > lovastatin, pravastatin > fluvastatin). In all probability, they would provide differential benefits in increasing HDL-C concentrations as well. Triglyceride-lowering effects appear to be similar among the statins.
5. There are subtle differences among statins in nonlipid effects including atherosclerotic, antithrombotic, and antiinflammatory effects.[45-48,98] This is suggested by results of angiographic trials, incidence of acute ischemic events (myocardial infarction, stroke), and development of other atherothrombotic conditions.
6. The fungi-derived statins (lovastatin, pravastatin, simvastatin) studied in primary and secondary prevention trials showed a class effect (i.e., reduced risk of mortality and/or major coronary events). It can be argued that the reduction in mortality shown with atorvastatin supports the premise that synthetic statins may have similar class effects. Little or no data exist for fluvastatin and rosuvastatin. Prevention of clinical endpoints is a factor that must be resolved, and there are considerations besides cost and reductions in LDL-C. Reliance on surrogate markers is associated with several limitations. The extent to which benefits of treatment are related to specific statin, class effect, or change in lipid profiling remains unclear.
7. All statins are well tolerated and appear to have a similar incidence of adverse events. However, myopathy-related deaths due to cerivastatin have proliferated, a fact that distinguishes it from other statins.

Given the strengths and weaknesses of the current evidence, there are sufficient data to suggest several definitive differences among the statins. Therefore, appropriate selection and/or substitution between the agents may be permissible, but should be done with caution. This, however, remains unresolved. Subtherapeutic efficacy, such as the failure to achieve National Cholesterol Education Program goals after conversion from a more potent to a less potent statin, is a major consideration.[122] In addition, there is a theoretical concern of precipitating myopathy and possible rhabdomyolysis after substitution, especially if statins are combined with other drugs metabolized through the cytochrome P450 system.[12-14] Other complications, including thrombotic stroke, have been reported.[122]

While newer statins should be evaluated in trials that demonstrate equivalence or superiority to older members of the class, this may not be feasible or affordable. Current National Cholesterol Education Program Adult Treatment Panel III cholesterol guidelines take no position on the class effect of statins.[22] This does not imply that there is no optimal statin for a particular patient, especially in the presence of comorbid conditions and the potential for drug interactions. In the future, professional organizations should take positions on class effect and the therapeutic interchangeability of statins.

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EXTRACTO

OBJETIVO: Repasar la literatura relevante y opinar sobre el efecto de clase de los inhibidores de la reductasa 3-hidroxi-3-metilglutaril-coenzima A (estatinas).

FUENTE DE DATOS: Se identificaron artículos primarios y de repaso por búsqueda de MEDLINE (julio 1990–2002).

SELECCIÓN DE ESTUDIOS Y EXTRACCIÓN DE DATOS: Se repasaron editoriales, estudios, y artículos de repaso relacionados al efecto de clase o al intercambio terapéutico de las estatinas. También se incluyó información relevante al tópico.

SÍNTESIS: Aunque las estatinas comparten las acciones comunes principales, tienen diferencias clínicas importantes en términos de eficacia y seguridad. A dosis fijas o aceptables, rosuvastatina, atorvastatina, y simvastatina producen una mayor reducción en colesterol y lipoproteínas de baja densidad comparado con otras estatinas. Algunas estatinas han mostrado reducción en mortalidad cardiovascular y total. Las estatinas difieren en su estructura, farmacocinética, potencia, y tasa de metabolismo, y algunas o todas estas diferencias pueden tener significancia clínica. Aunque inclusive, diferencias leves en los efectos no-lípidos de algunas estatinas puede haber contribuido a los beneficios positivos observados en estudios clínicos. Como resultado de las muertes relacionadas a fármacos, cerivastatina fue removida voluntariamente del mercado, lo que puede poner en dudas si es posible o no intercambiar terapéuticamente (por su efecto de clase) entre las estatinas.

CONCLUSIONES: A pesar de la competencia por el mercado y de las estrategias tratando de identificar diferencias en el valor terapéutico, se han llevado a cabo pocas comparaciones detalladas las estatinas. Los datos limitados disponibles sugieren que las estatinas no son intercambiables terapéuticamente.

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RÉSUMÉ

OBJECTIF: Revoir la littérature pour évaluer s'il existe un effet de classe pour les inhibiteurs de la 3-hydroxy-3-méthylglutaryl-coenzyme A réductase.

SOURCES DES DONNÉES: Littérature primaire et articles de revue identifiés en utilisant la banque de données MEDLINE durant la période de 1990 à juillet 2002.

SÉLECTION DES ÉTUDES: Les éditoriaux, les études cliniques, et les articles de revue décrivant les effets de classe ou si les différentes statines sont interchangeables ont été évalués.

ANALYSE DES DONNÉES: Même si les statines partagent le même mécanisme d'action, ils possèdent des différences cliniquement importantes au niveau de leur efficacité et de leur sécurité. À des posologies fixes, la rosuvastatine, l'atorvastatine, et la simvastatine produisent un effet plus marqué quant à la diminution du taux de cholestérol de lipoprotéines de faible densité comparativement aux autres molécules. Certaines statines ont démontré une réduction de la mortalité cardiovasculaire ou de la mortalité totale. Il existe des différences dans la structure chimique, les propriétés pharmacocinétiques, la puissance, et le métabolisme des différentes statines. Des différences subtiles dans les profils non lipidiques pourraient expliquer certains effets positifs observés dans les études cliniques. La cerivastatine a été récemment retiré volontairement du marché suite à plusieurs décès ce qui remet en question la problématique à savoir si les statines sont interchangeables.

CONCLUSIONS: Les auteurs concluent que compte tenu d'études cliniques limitées, les statines ne sont pas interchangeables.

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