REVIEW ARTICLE

Drug Safety 2006; 29 (5): 421-448
0114-5916/06/0005-0421/$39.95/0

Overcoming 'Ageism' Bias in the Treatment of Hypercholesterolaemia

A Review of Safety Issues with Statins in the Elderly

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Abstract

Atherosclerosis is a progressive, lifelong condition that is the leading cause of death among middle-aged and elderly individuals aged ≥65 years. Up to 80% of elderly patients are found to have evidence of obstructive coronary heart disease at autopsy. Demographic trends, including the advancing median age and life expectancy of Western societies, suggest that a large share of the burden of atherosclerotic plaque is likely to be borne by elderly individuals. These trends are in part due to increases in a number of chronic diseases associated with adverse cardiovascular outcomes, including metabolic syndrome, diabetes mellitus and chronic kidney disease. Because the elderly have a higher attributable risk of coronary heart disease as a result of hypercholesterolaemia, more coronary deaths and overall events can be prevented via treatment in this age group compared with younger persons with hypercholesterolaemia. The efficacy, safety and tolerability of HMG-CoA reductase inhibitors (statins) have been confirmed in randomised,

controlled, multicentre trials involving large numbers of patients aged ≥65 years. Although muscle symptoms such as myalgia are relatively common adverse events, more severe signs of myolysis such as myopathy and rhabdomyolysis are rare, but their risk is elevated by conditions (e.g. concomitant medications) that increase the systemic exposure of these agents. Statins differ in their susceptibility to increases in systemic exposure, but most statins have been demonstrated to be well tolerated and safe when administered to elderly patients. These favourable clinical findings should help clinicians counter highly prevalent 'ageism' bias in statin prescribing, whereby elderly patients, particularly those at highest cardiovascular risk, are often denied the benefits of statins without any meaningful foundation.

Approximately 75% of deaths due to myocardial infarction (MI) occur in patients aged ≥65 years.[1] Age is also the most heavily weighted coronary risk factor in Framingham risk models. Because the elderly have a higher attributable risk than their younger counterparts, more coronary events, including deaths, can be prevented by treating hypercholesterolaemia in this age group. In the Systolic Hypertension in the Elderly Program (SHEP), each 40 mg/dL (1.03 mmol/L) increase in total cholesterol level was associated with a 20% increase in coronary risk.[2]

Elderly patients comprised substantial proportions of the populations deriving significant clinical benefits from treatment with HMG-CoA reductase inhibitors (statins) in randomised, controlled, multicentre trials, such as the Heart Protection Study.[3] In a number of multicentre trials involving statins, numbers of patients needed to treat to benefit (NNT_B), to avert a single coronary event, including death, were similar or lower in the elderly than in younger patients.

Should effective care and compelling clinical benefits be withheld from patients on the basis of advanced age? If current prescribing practices are any indication, this would appear to be the prevailing view: all other factors being equal, patients aged >65 years are less likely to receive a statin prescription than younger patients. This pattern is consistent with a larger trend towards reducing statin prescribing as absolute coronary risk increases, such that patients at highest risk (i.e. those with coronary heart disease [CHD]) are least likely to receive treatment for hypercholesterolaemia.[4]

1. Dimensions of 'Ageism' in the Treatment of Hypercholesterolaemia

CHD and cerebrovascular disease (e.g. stroke) are leading causes of death, morbidity and healthcare expenditures in the elderly, and yet are vastly undertreated in this age group. The incidence of CHD peaks in patients aged ≥65 years;[5] CHD is the primary cause of mortality and morbidity in the elderly, and cerebrovascular diseases (e.g. stroke) rank third.[6]

1.1 Increasing Age, Increasing Chronic Disease Burden

Most coronary events and CHD deaths occur in elderly persons.[6] Each year, heart diseases (including heart failure) cause 612 199 deaths in adults aged ≥65 years, or 1808 deaths per 100 000 Americans (1.8% death rate) aged ≥65, including 6314 deaths per 100 000 Americans aged ≥85 (6.3% death rate).[6] Cerebrovascular diseases lead to another 140 488 deaths in elderly Americans each year.[6]

A major cause of morbidity, CHD is also associated with 2.7 million hospital discharges annually in elderly Americans.[6] Cerebrovascular diseases are associated with another 727 000 hospital discharges per annum.[6] Heart disease ranks third (behind arthritis and hypertension) among prevalent chronic conditions, affecting nearly 10 million elderly Americans.[6] Cerebrovascular diseases rank seventh, striking another 2.2 million elderly Americans. By one estimate, 67–75% of elderly Americans have either clinical CHD or subclinical atherosclerosis.[7]

The prevalence of stroke in US residents doubles in each decade after the age of 55 years.[8]

With the rising median population age and life expectancy, the atherosclerotic disease burden is likely to be borne increasingly by elderly Americans in the future. Since 1850, life expectancy has doubled, from approximately 40 to >80 years.[9] The number of US residents aged ≥65 years is expected to more than double from the year 2000 to 2050: from 35 million Americans (12.4% of total) in 2000 to ~55 million (16.3% of total) in the year 2020 and to ~87 million (20.7%) in the year 2050.[10] Octogenarians will comprise the fastest-growing age group. Although they now comprise only 5% of the US population, octogenarians account for 20% of all hospitalisations related to MI and 30% of all MI-related hospital deaths.[1]

One of the biological foundations for increased absolute coronary risk with advancing age is that there is a slow but progressive accumulation of atherosclerotic plaques in coronary arteries throughout life. The probability of experiencing an acute coronary event is directly proportional to the total 'burden' of coronary plaques.[11] Added to this burden, coronary artery calcification parallels the development of atherosclerotic plaques. Coronary calcium is correlated with atherosclerotic plaque severity by coronary angiography and at autopsy.[12-16] Although age may be perceived as a surrogate for plaque burden, more widespread use of noninvasive testing, such as electron beam computed tomography and carotid sonography, could assist in global risk assessment, whereby a patient would be "as old as his/her coronary arteries".[11]

With advancing age, patients are also increasingly prone to several conditions that elevate cardiovascular risk: metabolic syndrome, diabetes mellitus and chronic kidney disease (CKD). Among the approximately 64 million American adults with metabolic syndrome in the year 2000, the prevalence increased nearly 3-fold from age 20–29 to age ≥60 years: from 17.9% to 51.3% in women and from 14.8% to 40.0% in men.[17] Thus, nearly half of all Americans aged ≥60 years have metabolic syndrome. The dyslipidaemia associated with metabolic syndrome typically involves low serum levels of high-density lipoprotein cholesterol (HDL-C), as well as elevations in the levels of triglycerides and small, dense low-density lipoprotein (LDL) particles especially susceptible to oxidative modification. In 2002, cardiovascular diseases caused more deaths in women (493 623) than men (433 825).[18] Coronary heart disease rates in postmenopausal women are up to 3-fold higher than in premenopausal women. In women aged ≥65 years, the annual number of deaths due to cardiovascular diseases (442 000) is more than twice the number of deaths due to cancer (185 000) [figure 1].[18]

In the wake of the HERS (Heart and Estrogen/Progestin Replacement Study) and Women's Health Initiative, which demonstrated unanticipated increases in adverse cardiovascular events in women receiving combination hormone therapy, "there is a heightened need to critically review and document

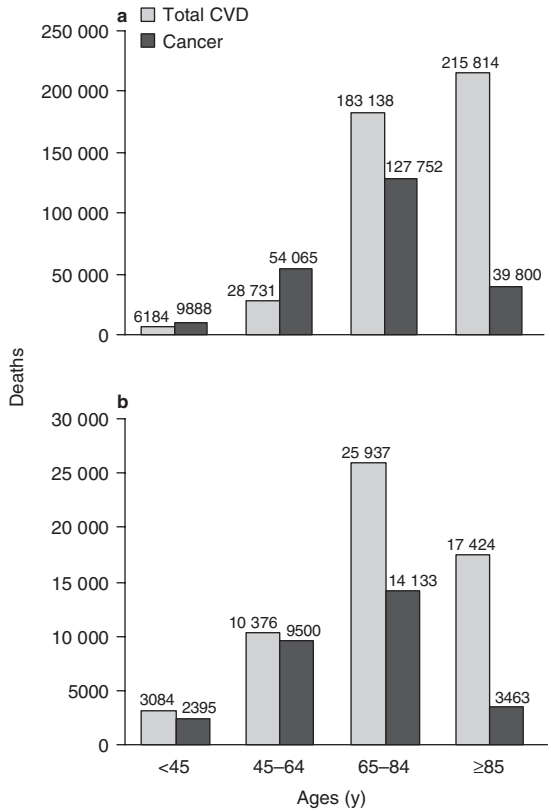

Fig. 1. Total number of deaths from cardiovascular diseases (CVD), including congenital cardiovascular defects, and cancer for (**a**) White and (**b**) Black women by age, US, 2001 (reproduced from American Heart Association,[18] with permission. © 2005, American Heart Association. www.americanheart.org).

strategies to prevent [cardiovascular disease] in women," according to recent consensus evidence-based guidelines.[19] Many postmenopausal women who previously relied on hormone replacement therapy for cardioprotective effects have yet to find other therapies for coronary prevention. However, statins conferred significant protection versus cardiovascular/thromboembolic events in HERS[20] and are considered first-line therapy for coronary prevention in postmenopausal women.[21]

One-year mortality following an MI is higher in women (38%) than men (25%), and 64% of women with sudden coronary death have no prior symptoms.[18] Yet, in a recent survey, only 46% of women identified CHD as a leading cause of death and only 38% reported that their physicians had ever discussed heart disease with them.[22] In addition, women at high risk are substantially less likely to be assigned by primary-care physicians to a higher-risk category than men, given similar risk profiles. Older high-risk women were also significantly less likely to receive dietary counselling and recommendations for weight control than their younger counterparts.[22]

Another disease of aging, CKD also predisposes older individuals to adverse cardiovascular outcomes. Characterised by reduced glomerular filtration rate (GFR) or proteinuria, CKD has recently emerged as an independent cardiovascular risk factor. In the recent VALIANT (Valsartan in Acute Myocardial Infarction Trial) study, each 10-unit decline in GFR below a value of 81.0 mL/min/1.73m^2 was associated with a 10% excess risk of death or cardiovascular complications (e.g. reinfarction, congestive heart failure and resuscitated arrest).[23] In the VALIANT study, the mean age increased with declining GFR. Mean age rose from 59.6 years in post-MI patients with GFR ≥75.0 mL/min/1.73m^2 to 73.3 years in those with GFR <45.0 mL/min/1.73m^2.[23]

Reduced apolipoprotein A-I and A-II levels, coupled with increased oxidative stress, lipoprotein oxidation and attendant atherosclerosis, justify categorising CKD as "the kidney manifestation of the systemic burden of vascular and endothelial disease."[24] Both the National Kidney Foundation and an American Heart Association panel have recommended that CKD be considered a CHD risk equivalent, with targeting of LDL cholesterol (LDL-C) to <100 mg/dL (2.59 mmol/L).[25,26] Similarly, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC-7) stated that the presence of CKD justifies lower target blood pressures.[27]

1.2 The Dimensions of Hypercholesterolaemia Undertreatment in the Elderly

According to guidelines from the Adult Treatment Panel III of the National Cholesterol Education Program, 10.5 million elderly Americans are eligible for treatment, including 4 million targeted for reduction of LDL-C to the aggressive goal of <100 mg/dL (2.59 mmol/L).[28,29] Although statin use in the elderly has increased in North America,[30] studies have demonstrated an inverse relationship between statin treatment and advancing age. A similar inverse relationship exists between absolute coronary risk and the likelihood of receiving a statin prescription.[4]

Relative to those aged <65 years, individuals aged 65–74 years are 36–47% less likely to receive a statin, and those aged ≥75 are 84–89% less likely.[31,32] In a recent North American survey,[33] only 19% of patients with CHD received statin prescriptions. The likelihood of statin treatment was approximately 6% lower for each year of increase in age over 65 years, as well as for each 1% increase in predicted 3-year mortality risk. Among patients aged 75–80 years, 29% of those at low coronary risk, 19.0% of those at intermediate risk and 15% of those at high risk received statin prescriptions. Among patients aged >80 years, these proportions were 13.5%, 6.6% and 4.4%, respectively.[33] As shown in figure 2, the probability of statin prescribing declined as a function of increasing age, and at all ages, patients at higher baseline coronary risk were less likely to receive a statin.[33]

Similar findings have been reported in the UK[31,32,34] and Europe.[35] In a recent European survey of patients with acute ischaemic stroke or transient ischaemic attack, the likelihood of receiving a statin at hospital discharge was 50% lower in patients aged 75–84 years and 80% lower in those aged

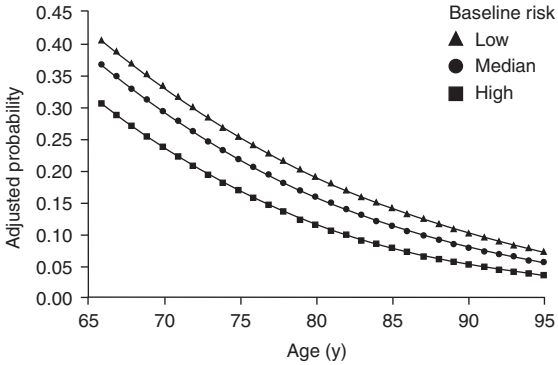

Fig. 2. Relationship of adjusted probability of receiving statins with age according to baseline risk (reproduced from Ko et al.,[33] with permission. ©2004, American Medical Association. All rights reserved).

≥85 years compared with patients aged <55 years.[35]

1.3 Potential Reasons for HMG-CoA Reductase Inhibitor (Statin) Undertreatment in the Elderly

The idea that cholesterol level might be less predictive of CHD in the elderly, or even that hypercholesterolaemia is 'protective' against mortality in these individuals, is prevalent among physicians, possibly in part as a result of certain epidemiological data. Various studies have demonstrated that there is either no significant association between elevated levels of serum total cholesterol or LDL-C and mortality, or that an inverse relationship exists between serum cholesterol level and mortality in elderly individuals.[36,37]

Other epidemiological studies have suggested that hypercholesterolaemia protects against mortality in elderly individuals even after accounting for the possibility that a low cholesterol level is a marker of overall frailty by adjusting for serum albumin level or excluding persons with either low serum total cholesterol levels or short life expectancies.[38-41] In patients aged >85 years, high levels of total cholesterol were directly associated with longevity, and the investigators ascribed this relationship to a lower mortality due to cancer and infection in those with elevated cholesterol levels.[41]

On the other hand, evidence from randomised, controlled, multicentre trials involving large numbers of elderly patients strongly suggests that these individuals derive similar cardioprotective benefits from long-term statin therapy to their younger counterparts. For instance, in the Heart Protection Study, which showed that 5-year treatment with simvastatin significantly lowered all-cause mortality (relative risk reduction 12.3%; p = 0.0003 vs placebo) because of a highly significant 18% proportional decline in coronary death rate (p = 0.0005 vs placebo), 10 697 (52%) of 20 536 high-risk individuals were aged ≥65 years, including 5806 (28%) aged ≥70 years.[3] The relative risk reduction in first major vascular events among individuals aged 65–69 years who were treated with simvastatin (vs placebo) was 23.2%, and the NNT_B was approximately 16; these values compare favourably with a 23.6% relative risk reduction and NNT_B value of approximately 19 in patients aged <65 years. Corresponding values in patients aged ≥70 years were a 17.8% relative risk reduction and a NNT_B value of approximately 20.[3]

Perhaps a second impediment to prescribing statins to elderly individuals at elevated coronary risk involves perceived disparities between outcomes observed in randomised controlled trials versus those observed in clinical practice. Randomised trials often have highly selected patient populations with demonstrated compliance and tolerance to statins, while patients in clinical practice are often sicker and less compliant with statin therapy. For instance, the Heart Protection Study excluded patients with chronic liver disease (either hepatitis or cirrhosis) or abnormal liver function tests, impaired renal function or severe nephropathy, heart failure, evidence of muscle problems, as well as patients taking concurrent treatments known to increase the systemic exposures of statins (e.g. ciclosporin). Liver enzymes, creatinine and creatine kinase levels were monitored during a 4-week placebo run-in, and only compliant individuals were randomised.[3] In the TNT (Treating to New Targets) study involving 10 001 patients with clinically evident CHD (mean age = 61 years), only patients who achieved a mean LDL-C level of <130 mg/dL following an 8-week open-label atorvastatin 10mg treatment interval were randomised to double-blind treatment with atorvastatin 10 or 80mg.[42]

2. Safety Issues Concerning Treatment of Hypercholesterolaemia in the Elderly

2.1 Overview

The chief safety concerns related to statin therapy are muscle injury, which may manifest as myalgia, muscle weakness or other symptoms (cramps, tenderness), or as signs of myolysis, including myositis (creatine kinase level elevations) and myopathy (creatine kinase level elevations together with muscle symptoms). Other potential concerns with statins include increases in hepatic transaminase levels, which are typically reversible and asymptomatic and occur in up to 3% of patients.[43,44] Other adverse events associated with statins include gastrointestinal complaints, headache and cutaneous effects.

2.2 Muscle Injury: Symptoms, Signs and Risk Factors

Statin-associated muscle injury represents a continuum. Approximately 1–5% of patients receiving statins experience myalgia, which is typically manifested as mild muscle aches or muscle weakness;[45] myalgia comprises 6–14% of all adverse events associated with statins.[46] Muscular symptoms are quite common in elderly patients and statin-induced myalgia may be somewhat difficult to distinguish from other musculoskeletal complaints.[47] As with other manifestations of muscle injury, myalgias frequently subside following reductions in medication doses or treatment discontinuation.

Myopathy has been defined in various ways, including "any noninherited disorder of skeletal muscle that causes proximal muscle weakness, with difficulty in arising from a chair or raising arms above the head".[44] For the purposes of this review, myopathy is defined as muscle discomfort together with ≥10-fold elevations in creatine kinase levels. However, skeletal-muscle biopsies may show evidence of myopathy in the absence of creatine kinase level elevations.[48]

The mechanism for statin-associated myopathy remains elusive. However, statins inhibit HMG-CoA reductase, the rate-limiting enzyme in cholesterol biosynthesis. Depletion of mevalonate derivatives, including ubiquinone (coenzyme Q10) and prenylated regulatory proteins, associated with statin treatment may lead to reduced function of the mitochondrial energy-producing apparatus in skeletal myocytes. Exercise, particularly eccentric exercise that requires the skeletal muscle to lengthen while also contracting (e.g. running downhill), may serve to 'unmask' statin-associated muscle injury.

On the basis of an analysis of randomised controlled trials, 7 (0.017%) of 42 323 patients treated with a statin experienced rhabdomyolysis as compared with 5 (0.012%) of 41 535 patients randomised to placebo.[45] Rhabdomyolysis is a potentially fatal syndrome characterised by myolysis and myoglobinuria, with electrolyte imbalances, cardiac arrhythmia, renal failure and/or disseminated intravascular coagulation. Fatalities due to statin-associated rhabdomyolysis are exceedingly rare, in the order of <1 death per million prescriptions: 0 cases documented for fluvastatin, 0.04 per million prescriptions of pravastatin and atorvastatin, 0.12 per million prescriptions of simvastatin, 0.19 per million prescriptions for lovastatin and 3.16 per million prescriptions for cerivastatin, which was voluntarily withdrawn from worldwide markets in August 2001.[45,49]

Increasing age and female gender are considered risk factors for developing statin-associated myopathy.[46] The possibility of developing myopathy may be increased by either patient or statin factors that increase systemic exposure. Patient factors include age-related declines in renal and hepatic function. Because most statins are chiefly excreted via the liver, reduced hepatic function can in theory result in higher circulating levels of statins in the elderly. Active liver disease is a contraindication with each of the statins. However, statins have been used successfully in patients with stable liver disease such as chronic hepatitis B.

Hypothyroidism and concomitant treatment with cytochrome P450 (CYP) inhibitors, including large quantities of grapefruit juice, may also increase the risk of statin-induced myopathy. Pravastatin is not a CYP substrate and may thus be less susceptible to CYP drug-drug interactions. In addition, rosuvastatin is metabolised by CYP isoenzymes to a minimal extent, with only 10% of an administered rosuvastatin dose being recovered as metabolites.[50]

Aging in general is associated with physiological changes that can potentially alter drug metabolism. Reductions in lean body mass may result in decreased distribution of hydrophilic drugs, and increased body fat with increased distribution of lipophilic drugs. Renally cleared drugs may accumulate in those with decreased renal function, and likewise, hepatically cleared drugs are affected when metabolism in the liver is slowed. Decreased albumin levels decrease binding and increase free concentration of basic drugs; increased α-1 acid glycoprotein levels increase binding and decrease free concentration of basic drugs. Alterations in cardiac reserve and autonomic/baroreceptor function may put the patient at risk of heart failure and postural hypotension, respectively. Of course, multiple disease states are associated with the risks of polypharmacy in general.

Because statins other than pravastatin are highly protein-bound, decreases in serum protein levels may result in increased free concentrations of certain agents. Declines in lean body mass might be expected to result in reduced tissue distribution of hydrophilic agents, such as pravastatin and to a lesser extent rosuvastatin, while the sarcopenic obesity of advancing age might be associated with increased tissue distribution of lipophilic statins, such as atorvastatin and simvastatin.

Although statins are principally cleared by the liver, various degrees of impairment in GFR with CKD warrant dosage adjustments with certain statins and other medications for dyslipidaemia.[25] Renal function may also decline in patients with diabetes, which represents another risk factor for statin myopathy.

In addition, the elderly are often under polypharmacy, which may contribute to drug-drug interactions. The chief concerns centre on substrates for CYP metabolism. Atorvastatin, lovastatin and simvastatin are metabolised by CYP3A4, substrates of which include azole antifungals, HIV protease inhibitors, macrolide antibacterials and certain cardiovascular medications, such as verapamil and digoxin. Rosuvastatin and fluvastatin are metabolised by CYP2C9 and/or CYP2C19, substrates of which include S-warfarin, diclofenac and ticlopidine.

Although pravastatin is not an appreciable CYP substrate, permeation of pravastatin into and out of cells is via the canalicular-membrane organic anion transporter (OAT), of which ciclosporin is also a substrate; therefore, concomitant administration of this immunosuppressant (e.g. in patients undergoing transplantation) can increase systemic exposure to pravastatin.[51] For transport into hepatocytes, where statins inhibit cholesterol biosynthesis, certain statins depend on the OAT protein; however, skeletal myocyte membranes do not contain this transporter. Therefore, permeation of these cells by statins depends on solubility in the phospholipid bilayer. Lipophilic statins, such as atorvastatin, simvastatin and lovastatin, may be more soluble in cell membranes than more hydrophilic statins, such as pravastatin and, to a lesser extent, rosuvastatin.[46]

By inhibiting the glucuronidation of certain statins, fibric-acid derivatives, particularly gemfibrozil, may increase their systemic exposure and myopathic potential.[52] In a review of a US FDA adverse events reporting database, Thompson and coworkers[45] attributed 58% of cases of statin-induced rhabdomyolysis to concomitant medications affecting statin metabolism, including fibrates (38%), ciclosporin (4%), macrolide antibacterials (3%), digoxin (5%), warfarin (4%) and azole antifungals (1%).

A recent inception-cohort study involving 252 460 patients treated with lipid-lowering therapies isolated 24 cases of hospital admissions for rhabdomyolysis.[53] Ten of these cases involved cerivastatin, which was voluntarily recalled by its manufacturer in August 2001 because of reports of fatal rhabdomyolysis. For statin monotherapy, the incidence of hospitalised rhabdomyolysis was 0.44 per 10 000 person-years. However, this rose to 5.98 per 10 000 person-years when atorvastatin, pravastatin or simvastatin were combined with a fibrate. A recent report based on a review of FDA databases suggested that reports of rhabdomyolysis are less frequent when statins are administered with fenofibrate compared with gemfibrozil.[54]

In the inception-cohort study,[53] there was a >5-fold increased risk of hospitalised rhabdomyolysis in patients aged ≥65 years (relative risk [RR] = 5.4; 95% CI 1.3, 21.6) and a nearly 3-fold increased risk in patients with diabetes mellitus (RR = 2.9; 95% CI

0.7, 11.8). Compared with a patient receiving statin monotherapy, a patient aged ≥65 with diabetes mellitus who was treated with both a statin and a fibrate was at 48-fold increased risk. Notably, in this inception cohort, 49.1% of patients using fluvastatin were aged ≥65, the highest proportionate use among branded statins. Yet there were no cases of hospitalised rhabdomyolysis associated with fluvastatin treatment.

An early signal for the myopathic potential of cerivastatin appeared in elderly women. In a recent report concerning steps taken (or not taken) prior to the market withdrawal of cerivastatin, Psaty et al.[55] noted that an FDA medical review identified thin, elderly women as being at increased risk of creatine kinase level elevations nearly 1 year before cerivastatin was withdrawn. This FDA review followed a report by Insull et al.[56] of an 8-week study in which ≥10-fold elevations of creatine kinase levels were observed in 5 of 90 (5.6%) women aged >65 years taking 0.8mg of cerivastatin. In the review by Thompson and coworkers,[45] the majority of rhabdomyolysis cases reported to the FDA between 1990 and 2002 involved patients aged ≥51 years. However, adverse event reports to the FDA are subject to bias and should not be equated to incidences of adverse events in randomised controlled trials.

The risk of myopathy is increased with advancing age, female gender and renal or hepatic insufficiency.[46] In addition, properties of certain statins may render them more susceptible to myopathy, including higher systemic exposure, bioavailability and lipophilicity, limited protein binding and potential drug-drug interactions via CYP or glucuronidation pathways (table I).[44] For instance, both fluvastatin and pravastatin are short lived and have no circulating active metabolites, but fluvastatin is more extensively protein bound. Pravastatin is also considered hydrophilic, which may translate into a low propensity for penetrating the skeletal myocyte membrane.

Another hydrophilic statin, rosuvastatin is minimally metabolised via CYP isoenzymes but is the longest lived (half-life = 20.8 hours) statin.[44] Atorvastatin also has a long half-life (15–30 hours) and is lipophilic.[44] The other highly lipophilic statins are simvastatin and lovastatin, which are sub-

Table I. Clinical pharmacokinetics of HMG-CoA reductase inhibitors (statins) [reproduced from Bellosta et al.,[44] with permission][a]

Parameter	Statin						
	atorvastatin	fluvastatin	fluvastatin XL	lovastatin	pravastatin	rosuvastatin	simvastatin
T_{max} (h)	2–3	0.5–1	4	2–4	0.9–1.6	3	1.3–2.4
C_{max} (ng/mL)	27–66	448	55	10–20	45–55	37	10–34
Bioavailability (%)	12	19–29	6	5	18	20	5
Lipophilicity	Yes	Yes	Yes	Yes	No	No	Yes
Protein binding (%)	80–90	>99	>99	>95	43–55	88	94–98
Metabolism	CYP3A4	CYP2C9	CYP2C9	CYP3A4	Sulfation	CYP2C9, 2C19 (minor)	CYP3A4
Metabolites	Active	Inactive	Inactive	Active	Inactive	Active (minor)	Active
Transporter protein substrates	Yes	No	No	Yes	Yes/No	Yes	Yes
$T_{1/2}$ (h)	15–30	0.5–2.3	4.7	2.9	1.3–2.8	20.8	2–3
Urinary excretion (%)	2	6	6	10	20	10	13
Faecal excretion (%)	70	90	90	83	71	90	58

a Based on 40mg oral doses, with the exception of fluvastatin XL (80mg).

C_{max} = maximum concentration; **CYP** = cytochrome P450; **$T_{1/2}$** = half-life; **T_{max}** = time to maximum concentration; **XL** = extended release.

Table II. Reported cases of fatal rhabdomyolysis per number of prescriptions for HMG-CoA reductase inhibitors (statins) dispensed in the US from launches to May 2001 (reproduced from Staffa et al.,[49] with permission. © 2002 Massachusetts Medical Society. All rights reserved)

Statin	Date approved	Fatal cases of rhabdomyolysis	No. of prescriptions	Reporting rate of rhabdomyolysis
Lovastatin	8/31/87	19	99 197 000	1 in 5.2 million
Pravastatin	10/31/91	3	81 364 000	1 in 27.1 million
Simvastatin	12/23/91	14	116 145 000	1 in 8.3 million
Fluvastatin	12/31/93	0	37 392 000	0
Atorvastatin	12/17/96	6	140 360 000	1 in 23.4 million
Cerivastatin	6/26/97	31	9 815 000	1 in 316 000

strates for both CYP3A4 and glucuronidation pathways. On the other hand, these agents have the lowest bioavailability of the statins and are extensively protein bound (table I).[44]

Rather than pharmacokinetic properties, the ultimate arbiters for the safety of statins include overall frequencies of rhabdomyolysis and other potentially serious adverse events, as well as safety data on each statin in elderly patients. As shown in table II, no cases of fatal rhabdomyolysis associated with fluvastatin have been reported to the FDA since the launch of this statin in 1993 until May 2001, an interval that covers in excess of 37 million prescriptions.[49] One reported case of fatal rhabdomyolysis occurred per 23.4 million and 27.1 million prescriptions with atorvastatin and pravastatin, respectively, as compared with one case per 8.3 million prescriptions with simvastatin.[49]

In an update of statin clinical trials reviewed in a meta-analysis by Law et al.,[57] the rate of rhabdomyolysis was 0.02% in patients randomised to statins compared with 0.01% in placebo controls.[3,58-87] In addition, 0.2% of statin recipients and 0.2% of placebo controls experienced ≥10-fold elevations in creatine kinase levels. Finally, 1.2% of patients receiving statins and 1.1% of placebo controls experienced ≥3-fold elevations in hepatic transaminase levels. In general, those trials (i.e. TNT[42], A to Z,[86] Pravastatin or Atorvastatin Evaluation and Infection Therapy [PROVE-IT][70]) that used higher or maximum doses of statins showed a higher rate of transaminitis and myopathy.

2.3 Statins and Hepatotoxicity

Although asymptomatic elevations in liver enzyme levels are not uncommon in patients treated with statins and represent a class effect of this group of medications, clinically significant hepatic injury is exceedingly rare.[43] The incidence of alanine aminotransferase (ALT) level elevations >3 times the upper limit of normal (3×ULN) is generally <3%, with a minor dose-related trend.[43] By Hy's Law, drug-related hepatocellular injury is not present unless ALT or aspartate aminotransferase (AST) levels increase to >3×ULN and bilirubin levels to >2×ULN over a 12-month observation period. Such combined abnormalities with statins are even more infrequent than isolated elevations in transaminase levels.

There is no convincing association between advancing age or increasing statin dose and the risk of significant liver injury.[43,88] In addition, although drug interactions that increase the systemic exposure of statins may play a role in the development of myopathy with statins, there is no evidence that such interactions are involved in the pathogenesis of the rare liver injury associated with statin therapy.[43,44,88]

Typically, elevated transaminase levels decrease upon either discontinuing or reducing the dose of a statin. The natural history of elevated transaminase levels with continued statin administration is unknown. Significant liver injury associated with statin therapy, including lovastatin and atorvastatin, has been reported in the literature,[89,90] but as mentioned previously, studies suggest that such injury is quite rare. Based on reports to a proprietary worldwide database, the risk of fulminant liver failure attributable to lovastatin was 2 cases per 1 million patients (0.0002%).[43,89,91] Among 51 741 patients with liver transplantations between 1990 and 2002, 3 (0.006%) had acute liver failure presumably asso-

ciated with statin treatment, including two cases of acute liver failure attributed to treatment with cerivastatin.[92] In the rare cases of statin-associated hepatotoxicity, hepatocellular, cholestatic and mixed patterns of liver injury have been observed, and there has also been some suggestion that statins can either elicit or unmask autoimmune liver disease.[88,93,94] The Adult Treatment Panel III recommends obtaining an AST/ALT level at baseline, approximately 12 weeks after initiating statin therapy, then annually or more frequently depending on dose titration.[28]

3. Safety Profiles of Individual Statins

3.1 Atorvastatin

Plasma concentrations of atorvastatin are increased 30–40% in healthy individuals aged ≥65 years compared with younger adults.[95] One pharmacodynamic consequence of these increases is a more potent LDL-C-lowering effect at each atorvastatin dose. ACCESS (Atorvastatin Comparative Cholesterol Efficacy and Safety Study), a 54-week open-label trial of 1958 patients treated with atorvastatin 10mg, included 835 elderly patients (43%).[95] The mean decrease in LDL-C following 6 weeks of atorvastatin 10mg was 38.2% in elderly patients compared with 34.6% in younger patients. Plasma concentrations are also increased in the presence of chronic alcoholic liver disease. Systemic exposure is increased up to 4-fold in patients with Childs-Pugh A disease and 11-fold in those with Childs-Pugh B disease.[95]

Atorvastatin has the lowest proportionate renal excretion of all the statins (~2%), and no dosage adjustments are necessary in patients with CKD, including GFR as low as <15 mL/min/1.73m^2.[25] On the other hand, doses of lovastatin, rosuvastatin and certain fibrates need to be halved (or reduced to 25% of usual dose) or avoided altogether in certain CKD patients.[25,50]

Other recent studies including large numbers of elderly patients have shown that atorvastatin tolerability and safety profiles are similar in the elderly compared with overall populations receiving atorvastatin in controlled clinical trials. In the recently reported TNT study involving atorvastatin 10 or 80mg in 10 001 patients with stable CHD, the mean population age was 61 years. Treatment-related adverse events and discontinuations were significantly higher in patients randomised to atorvastatin 80mg compared with atorvastatin 10mg.[42]

In TNT, a total of 7.2% of the atorvastatin 80mg group discontinued treatment because of adverse events compared with 5.3% of those in the atorvastatin 10mg group ($p < 0.001$). Both of these rates exceeded the <2% rates of treatment-related study discontinuations in registration trials.[95] Myalgias occurred in 4.8% of atorvastatin 80mg patients and 4.7% of atorvastatin 10mg patients (p-value = not significant [NS]), rates that fall within the range of 0–5.6% in controlled clinical trials.[95] Although a significantly higher proportion of patients receiving high-dose atorvastatin had persistent transaminase level elevations (1.2%) compared with their lower-dose counterparts (0.2%; $p < 0.001$), these rates were also not inconsistent with prior experience in clinical trials.[42] There were five cases of rhabdomyolysis (0.05%) in the total population, including three (0.06%) in the atorvastatin 10mg group.[42]

The CARDS (Collaborative Atorvastatin Diabetes Study) randomised 2838 patients aged 40–75 (mean = 62) years with type 2 diabetes mellitus to receive either placebo (n = 1410) or atorvastatin 10mg (n = 1428). In all, 1750 patients (62%) were aged ≥60 years, including 340 patients (12%) aged >70 years. Despite this relatively high representation of elderly patients, atorvastatin was well tolerated during the median follow-up of 3.9 years. Myalgias were reported by 5.1% of placebo controls and 4.3% of atorvastatin patients, with <1% of each group discontinuing treatment because of muscle adverse events; ≤1% of patients had 10-fold elevations in creatine kinase levels or 3-fold elevations in transaminase levels, and no patient developed rhabdomyolysis.[58]

Similarly, the ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm) study randomised 10 306 hypertensive patients aged 40–79 (mean = 63) years, of whom ~64% were aged >60 years. The number of serious adverse events and liver-function test abnormalities did not differ between the atorvastatin and control groups. A single case of rhabdomyolysis was observed in a man

with a recent febrile illness and high alcohol intake.[59]

Other adverse effects with atorvastatin include headache in up to 17% of patients; infection in up to 10%; abdominal pain, back pain, diarrhoea and rash in up to 4%; and sinusitis in up to 6.4%.[95] The chief interactions are with CYP substrates.[51,95] Although concomitant administration of the bile acid sequestrant colestipol lowers atorvastatin plasma concentrations by ~25%, this combination potentiates LDL-C reduction compared with either treatment in isolation.[95]

Atorvastatin can increase digoxin concentrations at steady state by ~20% and also augment systemic exposure to certain oral contraceptives to a similar degree.[95] In a recent pharmacokinetic analysis, concomitant administration of atorvastatin with clarithromycin increased atorvastatin systemic exposure 4-fold, whereas an azole antifungal significantly augmented atorvastatin systemic exposure (by 47%) and prolonged its half-life (by 60%; p = 0.052).[51] Atorvastatin is the second-longest-lived statin, with a half-life of 15–30 hours compared with ~21 hours for rosuvastatin.[44] In FDA database reviews, atorvastatin treatment was associated with 383 reports (11.5%) of rhabdomyolysis out of 3339 total cases reported from 1990 to 2002, and 0.04 fatal cases of rhabdomyolysis per million prescriptions.[45,49]

3.2 Fluvastatin

A number of pharmacokinetic characteristics combine to limit the systemic exposure of fluvastatin. These traits include high hepatic first-pass extraction (40–70%), avid protein binding (>98%), low volume of distribution at steady state (0.35 L/kg), and relatively short half-life (0.5–2.3 hours for immediate release).[44,96] In addition, fluvastatin has no circulating active metabolites.

As mentioned in section 2.2, to date there has not been a single report of a case of fatal rhabdomyolysis among patients treated with fluvastatin.[49] In a further review of FDA data, Thompson and coworkers[45] showed that fluvastatin contributed by far the smallest number and proportion of cases of rhabdomyolysis of all the statins: 55 (1.6%) of 3339. Such reports are subject to potential bias and should not be equated with incidences in randomised controlled trials.

In addition, because fluvastatin is not an appreciable substrate for either CYP3A4 metabolism or glucuronidation, it has been safely administered in concert with fibrates to many elderly patients. Frequencies of ≥10-fold elevations in creatine kinase levels and/or muscle symptoms in patients receiving fluvastatin/fibrate regimens have been exceedingly low, in the order of ≤1%.[97,98] Finally, neither the frequencies nor the severities of adverse events appear to differ between patients receiving either immediate-release fluvastatin 20–80mg or extended-release drug (fluvastatin XL) 80mg.[99]

Because fluvastatin is cleared hepatically with ~6% of the administered dose excreted in the urine, dose adjustments for mild to moderate renal impairment are not necessary. However, fluvastatin at doses >40mg has not been evaluated in patients with severe renal impairment.[96]

An international study including 1229 elderly patients (mean age = 75.5 years) with primary hypercholesterolaemia was conducted in Europe and Israel and reported in 2003.[100] Patients were randomised to placebo (n = 622) or fluvastatin XL 80mg (n = 607) daily for up to 1 year. Frequencies of adverse events were low and similar between the fluvastatin and placebo groups. Nineteen fluvastatin patients (3.1%) discontinued treatment because of adverse events compared with 15 (2.4%) controls (p = NS). Similarly <3.3% of patients in both groups experienced drug-related adverse events and ≤0.3% reported serious adverse events.[100]

No single adverse event occurred in >1% of either elderly patients receiving fluvastatin or placebo controls, including urinary tract infection and dyspepsia in 0.7% of fluvastatin patients. There were no consecutive >3-fold liver transaminase level elevations or >5-fold creatine kinase level elevations at any time during the study.[100] In registration studies, the most frequent adverse events observed with fluvastatin have been upper respiratory tract infection in up to 16.2% of patients; headache in up to 8.9%; dyspepsia in up to 7.9%; flu-like syndrome in up to 7.1%; as well as diarrhoea, rhinitis and abdominal pain in up to 4.9% each.[96]

In a study of elderly patients with hypercholesterolaemia, Lye et al.[101] observed no serious adverse

events with fluvastatin treatment. Although one fluvastatin patient exhibited abnormal liver function after 6 weeks of treatment with fluvastatin and was withdrawn from the study, attribution to fluvastatin was not conclusive. Other adverse events by body system (regardless of causality) included musculoskeletal events in two fluvastatin patients (6.1%) compared with one placebo control (2.8%); CNS or psychiatric events (e.g. sleep disturbance, lethargy, depression) in eight fluvastatin patients (24%) compared with six (17%) controls; and skin disturbances (e.g. itch) in three (9%) fluvastatin patients compared with no placebo controls.[101]

In a more recent study, the PRIMO (Prédiction du Risque Musculaire en Observationnel) study, Bruckert et al.[102] reported muscle symptoms in 832 (10.5%) of 7924 hyperlipidaemic men and women receiving high-dose statin therapy on an outpatient basis in France. Nearly 40% of patients reported the use of analgesics to manage these symptoms and/or reported that these symptoms prevented even moderate exertion during activities of daily living. In this observational study, 5.1% of patients receiving fluvastatin XL 80mg reported muscular symptoms compared with 10.9% of patients receiving pravastatin 40mg, 14.9% of those receiving atorvastatin 40–80mg, and 18.2% of those receiving simvastatin 40–80mg.[102]

Fluvastatin has also been well tolerated in other studies involving large numbers of elderly patients as well as other populations at potentially increased risk because of chronic immunosuppressant therapy (renal transplant patients) or exposure to fibric-acid derivatives. The mean patient age in the LIPS (Lescol Intervention Prevention Study) trial was 60 years. A total of 174 (21.2%) of 822 fluvastatin patients discontinued prematurely as a result of adverse events, compared with 196 (24.0%) of 818 controls.[103] Deaths due to noncardiac causes occurred in 2.7% of fluvastatin patients and 3.0% of placebo controls, while cancers occurred in 5.6% and 6.0% of these groups, respectively. No patient treated with fluvastatin experienced either >10-fold creatine kinase level elevation or rhabdomyolysis. Persistent 3-fold elevations of transaminase levels occurred in 1.2% of fluvastatin patients compared with 0.4% of controls.[103]

Transplant atherosclerosis remains a serious clinical impediment, and premature cardiovascular disease in renal transplant recipients might be partly attributed to adverse lipid effects of anti-rejection regimens (e.g. ciclosporin, corticosteroids). The ALERT (Assessment of Lescol in Renal Transplantation) study demonstrated that treatment with fluvastatin 40–80 mg/day for up to 6 years significantly reduced the occurrence of cardiac death or nonfatal MI compared with placebo, with a 35% relative risk reduction and NNT_B value of 31 to avoid a single event.[87] Fluvastatin was well tolerated, with 15% of fluvastatin patients and 16% of placebo controls discontinuing treatment prematurely because of adverse events. Frequencies of creatine kinase or transaminase level elevations also did not differ between the two groups. A total of 12 fluvastatin patients (1.1%) exhibited >3-fold elevations in ALT levels compared with 17 placebo controls (1.6%). At least 10-fold elevations in creatine kinase levels occurred in three fluvastatin patients (0.3%) and one placebo control (0.1%). One patient in each of the placebo and fluvastatin groups developed rhabdomyolysis as the result of severe trauma.[87] The major importance of the ALERT study was that fluvastatin demonstrated no significantly increased myopathy or rhabdomyolysis despite the fact that all the patients were taking potentially dangerous drugs, such as ciclosporin, and were taking other drugs with serious potential drug interactions.

Benghozi et al.[104] conducted a pooled analysis of all fluvastatin studies conducted from 1987 to 2001, including a total of 11 006 patients of whom 8683 received fluvastatin. Of all patients, 3250 (30%) were aged ≥65 years. In this population, the frequencies of ≥5-fold elevations in creatine kinase levels were low and comparable to placebo in patients treated with fluvastatin: <2% in all age groups. Of all gender-age groups, elderly women had the lowest frequency of creatine kinase level elevations (≤0.2%).[104]

Fluvastatin is metabolised chiefly by CYP2C9 and, to a lesser extent, by CYP2C8 and CYP3A4.[96] As a CYP2C9 substrate, fluvastatin may interact with S-warfarin, which is often used to prevent stroke in many elderly patients with atrial fibrillation (among other indications).[96] Increased pro-

thrombin times and bleeding episodes have been observed in some patients receiving statins with coumarin anticoagulants.[96] Prothrombin times should be closely monitored when fluvastatin or other statin treatment is initiated or doses changed in patients receiving coumarin anticoagulants.[96]

Other potential interactions with CYP2C9 substrates include phenytoin, glibenclamide (glyburide) and diclofenac.[96] The proton-pump inhibitor omeprazole and histamine H_2-antagonists ranitidine and cimetidine increase fluvastatin systemic exposure by up to 33%.[96] As with atorvastatin, administration of immediate-release fluvastatin up to 4 hours after cholestyramine sharply decreases fluvastatin systemic exposure, but the two agents confer additive benefits to lipid profiles.[96] On the other hand, concomitant administration of fluvastatin with nicotinic acid (niacin), gemfibrozil or digoxin has no bearing on fluvastatin plasma concentrations.[96]

3.3 Lovastatin

In the AFCAPS/TexCAPS (Air Force/Texas Coronary Atherosclerosis Prevention Study) trial, which demonstrated that lovastatin reduced the risk of a first acute major coronary event in individuals with 'average' LDL-C and total cholesterol levels and low levels of HDL-C, 1416 (21.4%) of 6605 patients were aged ≥65 years.[60] Lovastatin was well tolerated. Approximately 14% of patients in both the lovastatin and placebo groups discontinued treatment because of adverse events, and both groups had similar numbers of serious adverse events. Myalgias led to treatment discontinuation in 0.3% of actively treated patients and placebo recipients, but there were no cases of myopathy in either treatment arm. Elevations in creatine kinase level to >10×ULN occurred in <1% of patients randomised to either lovastatin or placebo. Among the three cases of rhabdomyolysis reported, two occurred in the control group. Fatal and nonfatal cancer (aside from nonmelanoma skin cancers) occurred in 15.1 per 1000 patient-years in the lovastatin group and 15.6 per 100 patient-years in the placebo group. In both the lovastatin (0.6%) and placebo (0.3%) treatment arms, consecutive elevations in AST or ALT levels to >3×ULN occurred in <1% of patients, with no trend between elevations in transaminase level and final lovastatin dose.[60]

Other safety data concerning lovastatin derive from the EXCEL (Expanded Clinical Evaluation of Lovastatin) trial, a randomised double-blind placebo-controlled study with follow-up data through 2 years.[61] In this efficacy and safety follow-up study involving 8245 patients with moderately severe hypercholesterolaemia, including 977 subjects who were entered into year 2, the mean age was 55 years for men (53% of participants) and 60 years for women. Lovastatin was well tolerated. Adverse events prompted study discontinuation during year 2 in 4% of placebo recipients, 2% of patients receiving lovastatin 20mg twice daily, and 6% of patients receiving lovastatin 40mg once daily. Drug-related adverse events led to treatment discontinuation in ≤2% of patients in both groups. Serious adverse events occurred in 9% of placebo controls and 8% (lovastatin 40mg) to 10% (lovastatin 80mg) of actively treated patients in treatment year 2.

No patient receiving lovastatin 20mg once or twice daily experienced myopathy in either treatment year, nor did any patient experience rhabdomyolysis. The incidence of myopathy in treatment years 1 and 2 ranged from 0.2% in patients receiving lovastatin 40mg twice daily to 0.5% in those receiving lovastatin 40mg once daily. A total of 12.3% of placebo patients experienced muscle symptoms without elevations in creatine kinase level as compared with 9.6% (lovastatin 40mg) to 13.2% (lovastatin 20mg) of actively treated patients. Increases in creatine kinase level to >10×ULN occurred in 0.4% of placebo controls during years 1 and 2 as compared with 0.2% (lovastatin 20mg) to 1.0% (lovastatin 20mg twice daily) of actively treated patients.[61]

Neither clinical hepatitis nor evidence of progressive liver disease was observed in any patient over the 2-year study interval.[61] The cumulative incidence of consecutive transaminase level elevations to >3×ULN was 0.1% in both the placebo and lovastatin 20mg groups, 0.9% in subjects receiving lovastatin 40mg daily and 1.9% in those receiving lovastatin 80mg. Single >3-fold elevations in transaminase levels during years 1 and 2 occurred in 3.6% of the placebo group and up to 4.9% of lovastatin-treated patients (in the lovastatin 40mg twice-daily group), while single >2-fold elevations occurred in 2.9% of placebo recipients and up to

7.0% of lovastatin-treated patients (in the lovastatin 40mg twice-daily group).[61]

3.4 Pravastatin

This non-CYP inhibitor has the smallest volume of distribution of all statins other than fluvastatin. Pravastatin also has the highest proportion of clearance via the renal route: approximately 20%.[105] Following intravenous administration of radiolabelled pravastatin, 47% of total body clearance by healthy volunteers was via renal excretion. Manufacturer labelling advises close monitoring of patients with renal impairment when receiving pravastatin.[105]

In the PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) study involving elderly individuals, similar proportions of patients experienced adverse events in the pravastatin and placebo groups. Only about 1% of patients in each group reported myalgia. No cases of rhabdomyolysis or >10-fold increases in creatine kinase level were reported in either group. Only one patient in each group (0.03%) had >3-fold rises in hepatic transaminase levels.[62]

There was a slight but statistically significant imbalance in new cancer diagnoses in the pravastatin group compared with placebo (hazard ratio = 1.25; 95% CI 1.04, 1.51; p = 0.020). Among the entire (intent-to-treat) population, 8.5% of patients receiving pravastatin had new cancers compared with 6.8% of placebo controls. Gastrointestinal cancers were approximately 46% more frequent in the pravastatin group (p = 0.053).[62] However, in a meta-analysis involving only trials with at least 1000 patients followed for at least 4 years (n = 8745), there were no differences in the absolute risks of cancers (or a slight imbalance favouring statins) between statin and placebo groups.[106] Across these studies, there was a 1.5% decrease in all-cause mortality favouring the statin treatment groups compared with placebo.[106]

In the elderly subgroup analysis of the LIPID (Long-Term Intervention With Pravastatin in Ischaemic Disease) trial, rates of adverse events did not differ between the pravastatin and placebo control groups, either in elderly patients or the entire treatment population.[107] In this study, relative risks for a number of adverse events between the pravastatin and placebo groups were <1.00 in elderly patients, including events affecting the liver (RR = 0.92; 95% CI 0.65, 1.30), as well as the muscular system (RR = 0.92; 95% CI 0.77, 1.10) or gastrointestinal tract (RR = 0.89; 95% CI 0.77, 1.01). On the other hand, adverse effects of the renal or genital systems were more frequent in elderly patients treated with pravastatin (RR = 1.09; 95% CI 0.93, 1.28). Among the elderly, more pravastatin patients developed cancer compared with placebo patients, whereas the converse was true in younger patients. However, neither of these between-group differences in relative risk was significant, and a test for heterogeneity using age as a continuous variable was not significant.[107]

Of 3339 reports of rhabdomyolysis in the FDA database between 1990 and 2001, pravastatin was associated with 243 cases (7.3%), and the rate of fatal rhabdomyolysis was 0.04 per million prescriptions.[45,49] As mentioned section 2.2, concomitant administration of ciclosporin (but not clarithromycin, itraconazole or verapamil) elevates the systemic exposure to pravastatin, perhaps because both compounds are substrates for the canalicular multispecific OAT.[51] Other agents that can increase pravastatin systemic exposure or reduce urinary clearance include digoxin and gemfibrozil. Manufacturer labelling states that concomitant pravastatin and gemfibrozil is generally not recommended.[105] Pravastatin is considered to be the most hydrophilic statin.

3.5 Rosuvastatin

Larger numbers of elderly patients have been involved in clinical registration programmes for rosuvastatin than for any other statin.[108] In phase III trials, there was no upper limit on age and patients with stable concomitant illnesses (e.g. diabetes mellitus) and with mild to moderate renal impairment were included. In a report of phase II/III integrated safety data spanning 12 212 patient-years, Shepherd et al.[108] noted that both the type and frequency of adverse events were similar in patients irrespective of age group. There were also no important differences in frequencies of adverse events across various categories of renal and hepatic function or concomitant illness.

In this report involving 12 400 patients randomised to rosuvastatin 5–40mg, 6923 patients (56%) were aged ≥65 years, including 3029 (24%) patients who were aged ≥70 years. Treatment-related adverse events occurred in 16% of patients receiving rosuvastatin 5–40mg compared with 18% of placebo controls. A total of 3.2% of patients discontinued rosuvastatin because of adverse events compared with 4.7% of placebo controls.[108]

One case of myopathy occurred among patients receiving rosuvastatin 20mg (0.03%); however, rosuvastatin causality could not be definitively assigned because the patient had coxsackie B virus, which is associated with a range of muscle-related symptoms.[108] Rates of >10-fold elevations in creatine kinase level were 0.4% in patients receiving rosuvastatin 5 or 40mg and 0.2% in those receiving rosuvastatin 10–20mg. In active-comparator trials, 0.2% of rosuvastatin patients had >10-fold increases in creatine kinase level compared with 0.2% of those receiving simvastatin, 0.1% of those receiving atorvastatin, and 0% of those receiving pravastatin.[108]

The chief concern with rosuvastatin was dipstick-positive proteinuria in some patients randomised to the 80mg dose, which was ultimately withdrawn by the manufacturer. In the STELLAR (Statin Therapies for Elevated Lipid Levels Compared Across Doses to Rosuvastatin) study, in which ~29% of patients were elderly, two patients randomised to rosuvastatin developed acute renal failure of uncertain aetiology, one of whom required brief dialysis.[109] Approximately 7% of patients randomised to rosuvastatin 80mg reported myalgia, although this proportion was <2% in those receiving rosuvastatin 40mg. There were no cases of rhabdomyolysis, although one patient receiving rosuvastatin 80mg experienced a >10-fold increase in creatine kinase level. Dipstick-positive proteinuria occurred in 0.6% of placebo controls as well as 0.2% of patients receiving rosuvastatin 5mg, 0.6% of those receiving 10 mg, and 0.7% of those receiving rosuvastatin 40mg. Similar findings were observed in patients receiving atorvastatin, pravastatin or simvastatin.[109]

On the other hand, most of the proteins in the urine were lower-molecular-weight molecules (by gel electrophoresis) consistent with reduced tubular reabsorption rather than impaired glomerular filtration (glomerular leak). Dipstick-positive proteinuria was typically transient and reversible and was not associated with deteriorating renal function in long-term studies of at least 96 weeks' duration in any patients, regardless of age or baseline GFR above or below 60 mL/min/1.73m^2).[108]

No rosuvastatin dosage modification is necessary in patients with mild to moderate renal impairment. However, in patients with severe renal impairment (GFR <30 mL/min/1.73m^2), a starting dose of 5mg should be used and the rosuvastatin dose should not exceed 10mg daily.[50]

Rosuvastatin is the longest-lived statin, with a plasma half-life of approximately 21 hours.[44] Only a small proportion of rosuvastatin is metabolised (10%), and clearance is predominantly via the faecal route (90%). Plasma concentrations are similar in patients above or below the age of 65 years. Martin et al.[110] determined that advancing age had no clinically meaningful effect on rosuvastatin pharmacokinetics: the systemic exposure (area under the curve [AUC]) was 6% lower and the maximum serum concentration (C_{max}) was 12% lower in elderly patients compared with their younger counterparts. Rosuvastatin is a CYP2C9 and CYP2C19 inhibitor. Concomitant medications that can substantially elevate rosuvastatin concentrations include ciclosporin and gemfibrozil. Although concomitant administration of warfarin with rosuvastatin did not alter warfarin concentrations, the international normalised ratio did increase.[50]

Partly as a result of a petition by Public Citizen, a US advocacy group, requesting that the FDA remove rosuvastatin from the market, the safety profile of this statin has come under intense scrutiny. In a letter to Public Citizen dated March 11 2005, Steven Galson, MD, MPH, who is Acting Director of the FDA Center for Drug Evaluation and Research, noted that 0.3–0.43 cases of rhabdomyolysis were reported per 100 000 prescriptions during three different reporting time periods compared with 0.06 cases per 100 000 with atorvastatin (all doses) and 15.2 cases per 100 000 with cerivastatin (0.8 mg), which was voluntarily withdrawn from the market.[111] Of the reported eight domestic cases of myopathy or rhabdomyolysis, three involved patients started on therapy at the 40mg dose, which is

contrary to product labelling.[50,111] Two of these cases involved concomitant administration of ciclosporin, which increases the systemic exposure of all statins; the US label recommends a dose of 5mg in patients receiving ciclosporin.[50] In addition, rosuvastatin was initiated at a dose of 20mg in one patient with chronic renal failure, whereas the label recommends a 5mg starting dose.[50]

As shown in figure 3, the benefit/risk ratio for rosuvastatin treatment is similar to those for the other statins with regard to the risk of >10-fold elevations in creatine kinase level as a function of LDL-C-lowering capacity.[111,112] This was the position adopted by the FDA, which recommended minor labelling changes and continued post-marketing surveillance for reports of rhabdomyolysis.

The second concern cited by Public Citizen in its petition centered on renal insufficiency or failure associated with rosuvastatin: cases of dipstick-positive proteinuria with and without haematuria, chiefly in open-label studies without placebo control, associated with rosuvastatin. As mentioned previously, the low molecular weights of most proteins pointed to a tubular rather than a glomerular origin. Indeed, a recent placebo-controlled trial demonstrated that rosuvastatin treatment for up to 3.8 years was associated with an increase of 5 mL/min/1.73m^2 in GFR, and this potentially renoprotective effect did not vary in patients aged ≥65 years compared with

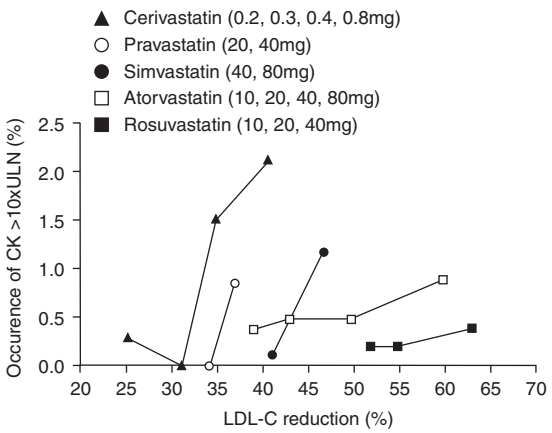

Fig. 3. Low-density lipoprotein cholesterol (LDL-C) reductions versus creatine kinase (CK) level elevations >10 times the upper limit of normal (ULN) for cerivastatin, pravastatin, simvastatin, atorvastatin and rosuvastatin.[111]

their younger counterparts.[113] Similarly, the FDA response to the Public Citizen petition cites manufacturer data showing an average decrease in serum creatinine level in patients treated with high doses of rosuvastatin.[111]

The FDA pointed to several lines of evidence in rejecting Public Citizen's petition with respect to renal adverse events with rosuvastatin.[111] First, in the original rosuvastatin new drug application (NDA) review, ≥2+ proteinuria was observed in <5% of patients receiving atorvastatin, pravastatin, rosuvastatin up to 40mg, simvastatin or placebo (figure 4).[111] Only the rosuvastatin 80mg dose, which is not marketed, was associated with a significantly higher incidence of proteinuria. Secondly, in an *in vitro* model (opossum proximal tubular epithelial kidney cell line), inhibition of HMG-CoA reductase by a number of statins in renal tubular cells led to concentration-dependent blockade of protein uptake, which was reversed by adding mevalonate. These findings suggest a pharmacological class effect of statins on proximal tubular protein reabsorption.[111]

Although >15% of patients receiving rosuvastatin 80mg manifested proteinuria, <5% of those receiving either other statins or rosuvastatin at lower, marketed doses had proteinuria.[111] In addition, 0.2–4.2% of patients receiving rosuvastatin at doses of 5–40mg experienced proteinuria together with >30% elevations in creatinine level. Proteinuria together with haematuria was much less common, occurring in 0.1–1.6% of patients. Finally, only 3 of ~6000 rosuvastatin patients (0.05%) experienced combined haematuria and proteinuria in concert with increases in creatinine level. None of these patients developed renal failure.[111] Although five patients developed renal insufficiency or failure with rosuvastatin in clinical trials, all cases were confounded by comorbid medical conditions, such as critical illness, diabetes or recent major surgery, which could contribute to the development of renal disease in their own right.

Overall rates of renal failure and insufficiency in nearly 18 000 patients studied in post-marketing trials were 0.08% and 0.04%, respectively, and none of these cases were attributed by investigators to the use of rosuvastatin.[111] In FDA databases, there were 30 domestic reports of renal damage with

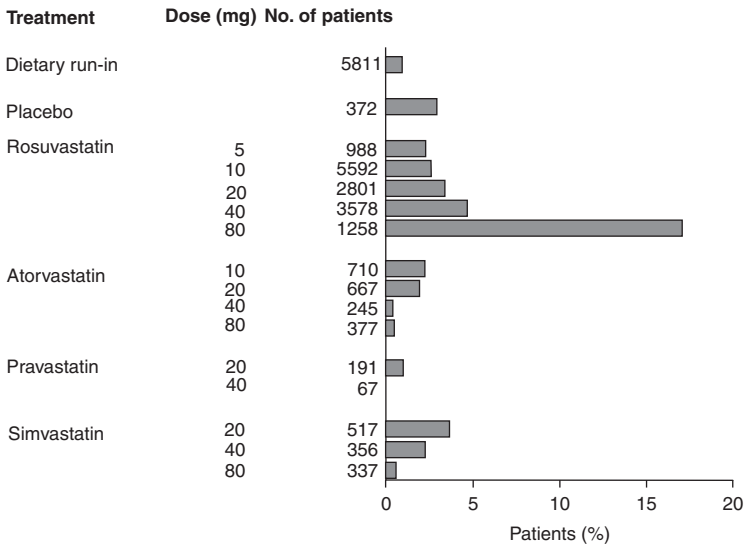

Fig. 4. US FDA advisory committee presentation of the incidence of proteinuria at any study visit in double-blind, controlled studies.[111]

rosuvastatin out of >6 million prescriptions, for a report rate of 0.5 per 100 000 prescriptions.[111] This was >12-fold higher than the report rate for renal injury with atorvastatin: six reports out of >13 million prescriptions, for a report rate of 0.04 per 100 000 prescriptions. Given many potential limitations and biases of voluntary post-marketing surveillance reports, the FDA did not view this disparity as meaningful.

In a recent analysis of the FDA Spontaneous Reporting System (SRS) and Adverse Events Reporting System (AERS) databases, Alsheikh-Ali and colleagues[114] showed that a 'composite endpoint' of adverse event reports including rhabdomyolysis, proteinuria, nephropathy or renal failure was significantly more frequent with rosuvastatin than with simvastatin, pravastatin or atorvastatin ($p < 0.001$ for each comparison) during the first year that rosuvastatin was available in the US. When these adverse event reports were compared between the first year of marketing for rosuvastatin and the other statins, the rate of composite adverse events was significantly higher with rosuvastatin compared with either pravastatin or atorvastatin ($p < 0.001$ for each) but significantly less than with cerivastatin ($p < 0.001$).[114]

Although the rate of rosuvastatin-associated rhabdomyolysis adverse event reports was significantly higher than with simvastatin, pravastatin or atorvastatin based on reports received during the first year of marketing for each statin, reports of rhabdomyolysis were still significantly less than with cerivastatin during its first year of marketing ($p < 0.001$).[114]

An accompanying editorial by Grundy seriously called into question these findings.[115] Perhaps most fundamentally, spontaneous adverse event reporting with rosuvastatin may be biased upward by the media attention focused on this agent, partly as the result of the petition for market withdrawal of rosuvastatin by Public Citizen. In addition, the FDA reviewed adverse event reports for rosuvastatin over the same period and did not find any "signal" indicative of safety issues. The FDA AERS database also underwent substantial changes over the last several years, rendering comparisons of adverse event reports between different periods undesirable. The lack of a control group, variability in the level of detail reported, and deficiencies in reporting of confounding risk factors further weaken the inference of causality.

Grundy also questioned the wisdom of combining severe myopathy with an evidently innocuous type of proteinuria as well as the clinical meaning of statistically significant differences between adverse events reported very infrequently overall. For in-

stance, during the first 6 months of rosuvastatin availability, two cases of severe myopathy were reported to the FDA out of an estimated 763 000 prescriptions. Although the resulting rate (0.3 per 100 000 prescriptions) is approximately 5-fold higher than the rate with atorvastatin during the same interval (0.06 per 100 000 prescriptions), it is nearly two orders of magnitude lower than the rate observed with cerivastatin (15.2 per 100 000 prescriptions) during a comparable interval. The overall rate of severe myopathy with rosuvastatin in postmarketing studies was only 0.01%, which is within the frequency range reported with other statins.[115]

3.6 Simvastatin

Both simvastatin and its active metabolite simvastatin acid are highly protein-bound (~95%).[44,116] The acid metabolite can be glucuronidated, and the manufacturer's labelling urges clinicians to avoid concomitant use of simvastatin with gemfibrozil, another glucuronidation substrate.[116] Simvastatin is also a CYP3A4 substrate. Following submission of a supplemental NDA for simvastatin 80mg, the FDA mandated altered safety labelling concerning combinations of simvastatin with concomitant medications. The dose of simvastatin should not exceed 10mg daily in patients receiving concomitant ciclosporin or danazol and should not exceed 20mg daily in those receiving verapamil or amiodarone.[116] Concomitant treatment with certain azole antifungals and macrolide antibacterials, as well as HIV protease inhibitors, nefazodone, and large quantities of grapefruit juice, should be avoided.[116]

Although the rosuvastatin clinical registration programme involved the most elderly patients, the finding of no signal for increased adverse events in elderly patients undergoing treatment in the Heart Protection Study is reassuring.[3] Of the 20 536 high-risk individuals randomised in this study, 10 697 (52%) were aged ≥65 years. A total of 5366 elderly patients received care with simvastatin, including 2919 patients aged ≥70 years. In this study, 0.42% of all simvastatin patients had >4-fold ALT level elevations compared with 0.31% of placebo controls. Muscle symptoms were reported by similar proportions of patients in the simvastatin and control groups.[3]

Treatment was withdrawn prematurely because of muscle symptoms in 0.5% of each treatment group. Greater than 10-fold increases in creatine kinase level were observed in 0.11% of simvastatin patients and 0.06% of placebo controls. Myopathy defined by muscle symptoms together with >10-fold elevations in the level of creatine kinase were observed in 0.05% of simvastatin patients and 0.01% of controls. Finally, rhabdomyolysis occurred in 0.05% of simvastatin-allocated patients compared with 0.03% of placebo controls. No cases of rhabdomyolysis were fatal. In the aggregate, these exceedingly low frequencies of transaminase and creatine kinase level elevations as well as of myopathy and rhabdomyolysis, together with equal or superior benefits of lipid-lowering therapy in terms of coronary prevention, among >10 000 elderly patients in a prospective, randomised, placebo-controlled trial, make a strong case for treatment of high-risk elderly patients with a statin. Fewer than five simvastatin patients per 1000 had a creatine kinase level elevation, while five simvastatin patients per 10 000 had myopathy.[3]

Further, in the Scandinavian Simvastatin Survival Study, frequencies of adverse events were similar in men and women and in patients aged under or over 65 years.[117] In the elder subgroup, 5.4% of simvastatin patients discontinued treatment because of adverse events compared with 5.1% of placebo controls; in younger patients, corresponding values were 5.8% and 7.8%. Fewer than 1% of patients experienced serious drug-related adverse events with simvastatin or placebo in elderly patients (0.8%) or their younger counterparts (0.4%).[117]

In a review of FDA databases, 612 (18.3%) of 3339 reports of rhabdomyolysis were associated with simvastatin treatment and the rate of fatal rhabdomyolysis reports was 0.12 per million prescriptions.[45,49] Many patients who developed rhabdomyolysis in clinical studies involving simvastatin had complex medical histories, including renal insufficiency, typically as the result of long-standing diabetes; such patients need closer monitoring.[116] Patients should be advised of the risk of myopathy when simvastatin therapy is being initiated or increased in dose, and treatment should be suspended a few days before elective major surgery or in the event of supervening medical or surgical

conditions. Simvastatin treatment should also be administered with caution in patients consuming large quantities of alcohol and/or with a history of liver disease.[116]

4. Combination Lipid-Lowering Therapies

4.1 Statins/Ezetimibe

One strategy to limit statin doses, and thus also dose-related adverse effects such as myopathy, is through the use of adjunctive regimens, including statins combined with the cholesterol absorption inhibitor ezetimibe. In a pooled analysis of four randomised, double-blind, placebo-controlled studies involving 1861 patients with primary hypercholesterolaemia, statins/ezetimibe were generally well tolerated in elderly patients.[118] No patients had >10-fold creatine kinase elevations while receiving statins/ezetimibe regimens, and consecutive ≥3-fold elevations in transaminase levels were also infrequent (<2%). None of the 66 patients aged ≥75 years experienced consecutive ≥3-fold elevations in the levels of AST or ALT on concomitant statins/ezetimibe regimens. Adverse events considered by the investigator to be possibly, probably or definitely related to treatment were somewhat more frequent in older patients receiving statins/ezetimibe compared with their younger counterparts, occurring in 26% of patients aged ≥75 years compared with 19% of those aged <75 years. Corresponding frequencies of adverse events leading to discontinuation were 12% and 5%, respectively. These frequencies were somewhat higher than were observed in patients treated with statin monotherapy. A total of 12% of patients aged ≥75 years experienced treatment-related adverse events with statin monotherapy compared with 17% of those aged <75 years. Corresponding frequencies of discontinuations resulting from adverse events were 0% and 5%, respectively. There were no drug-related deaths, and serious adverse events occurred in ≤3% patients of any age receiving statins/ezetimibe therapy.[118]

About 5% of statins/ezetimibe patients aged <65 years discontinued treatment because of adverse events, compared with 3% of those aged ≥65 and 12% of those aged ≥75; corresponding percentages with statin monotherapy were 4%, 5% and 0%.[118] Some elderly patients with limited financial resources might be opposed to combination or other potentially costly regimens.

4.2 Statins/Fibrates

In certain patients with metabolic syndrome, diabetes and other forms of mixed dyslipidaemia marked by low levels of HDL-C as well as elevated levels of total cholesterol, LDL-C, triglycerides and small dense LDL particles susceptible to oxidation, concomitant statin/fibrate therapy is a rational alternative. Given the high prevalence of obesity, metabolic syndrome and diabetes in the US, together with the advancing median age and increasing life expectancy of the US population, substantial numbers of patients are likely to have these forms of dyslipidaemia, warranting consideration of statin/fibrate regimens.

In the recent inception-cohort analysis by Graham et al.,[53] the incidence of hospitalised rhabdomyolysis rose from 0.44 per 10 000 person-years for atorvastatin, pravastatin or simvastatin monotherapy to 5.98 per 10 000 person-years when these statins were combined with fibrates and to 1035 per 10 000 person-years (i.e. 1 per 10 person-years) when fibrates were combined with cerivastatin.

Despite these findings, there is considerable evidence to suggest that fibric-acid derivatives other than gemfibrozil, and statins other than cerivastatin (particularly fluvastatin), are associated with a lower risk of rhabdomyolysis in combination regimens. In a recent review of FDA databases, Jones and Davidson[54] reported that the number of reports of rhabdomyolysis per million prescriptions of cerivastatin combined with a fibrate was approximately 33 times lower with fenofibrate (140 per million prescriptions) compared with gemfibrozil (4600 per million prescriptions). The reporting rate was approximately 15 times lower with fenofibrate combined with all other statins (0.58 per million prescriptions) as compared with gemfibrozil/statin regimens (8.6 per million prescriptions).

Gemfibrozil, fenofibrate, and its active metabolite fenofibric acid are all substrates for glucuronidation before urinary excretion.[52,119] The

Table III. Profile of 601 reports of rhabdomyolysis associated with six HMG-CoA reductase inhibitors (statins) [reproduced from Corsini,[121] with permission of Springer Science and Business Media]

Statin	No. of cases (% of total)	No. of cases associated with potentially interacting drugs[a] (n)	
Simvastatin	215 (35.8)	Mibefradil (48)	Azole antifungals (4)
		Fibrates (33)	Chlorzoxazone (2)
		Ciclosporin (31)	Nefazodone (2)
		Warfarin (12)	Nicotinic acid [niacin] (2)
		Macrolide antibacterials (10)	Tacrolimus (1)
		Digoxin (9)	Fusidic acid (1)
Cerivastatin	192 (32.1)	Fibrates (22)	Macrolide antibacterials (2)
		Digoxin (7)	Ciclosporin (1)
		Warfarin (6)	Mibefradil (1)
Atorvastatin	73 (12.2)	Mibefradil (45)	Ciclosporin (5)
		Fibrates (10)	Digoxin (5)
		Macrolide antibacterials (13)	Azole antifungals (2)
		Warfarin (7)	
Pravastatin	71 (11.8)	Fibrates (6)	Digoxin (2)
		Macrolide antibacterials (6)	Mibefradil (1)
		Warfarin (5)	Nicotinic acid (1)
		Ciclosporin (2)	
Lovastatin	40 (6.7)	Ciclosporin (12)	Digoxin (2)
		Macrolide antibacterials (11)	Nefazodone (2)
		Azole antifungals (6)	Nicotinic acid (1)
		Fibrates (5)	Warfarin (1)
		Mibefradil (3)	
Fluvastatin	6[b] (1.7)	Fibrates (4)	
		Warfarin (2)	
		Digoxin (1)	
		Mibefradil (1)	

a Each case may be associated with one (or more) potentially interacting drug(s).

b The published number of cases is ten, but only six reports have now been verified as being associated with fluvastatin.

glucuronidation pathway of fibrates is shared with statins and largely accounts for the pharmacokinetic interaction between these classes of drugs. Of 601 cases of rhabdomyolysis with statins (table III), 215 (35.8%) were contributed by simvastatin, a higher number (and proportion) than the 192 (32.1%) cases contributed by cerivastatin. On the other hand, fluvastatin contributed only 6 verified cases, including 4 with concomitant fibrate therapy, while pravastatin contributed 71 cases (11.8%), including 6 with concomitant fibrate treatment; lovastatin contributed 40 cases (6.7%); and atorvastatin contributed 73 cases (12.2%), including 10 with concomitant fibrate treatment.[120,121]

Chang and coworkers[122] reported similar trends (table IV). Aside from cerivastatin, which was associated with approximately 1249 reports of rhabdomyolysis per 100 000 prescriptions of gemfibrozil/cerivastatin, simvastatin was associated with the highest rhabdomyolysis reporting rate when administered with gemfibrozil: 3.85 per 100 000 prescriptions, followed by lovastatin (2.84 per 100 000 prescriptions), pravastatin (0.14 per 100 000 prescriptions) and atorvastatin (0.50 per 100 000 prescriptions).[122] There were no cases of rhabdomyolysis associated with concomitant fluvastatin/gemfibrozil therapy.[122] These findings are consistent with clinical trials showing very low rates of creatine kinase level elevations and no reported cases of myopathy or rhabdomyolysis when fluvastatin was administered together with fenofibrate, bezafibrate or gemfibrozil.[97,98,123] Fluvastatin may be the safest statin when coadministered with a fibrate.

Table IV. Reporting rates (per 100 000 prescriptions) for US cases of rhabdomyolysis associated with HMG-CoA reductase inhibitors (statins): all cases[a] reported through July 31, 2001 (reproduced from Chang et al.,[122] with permission. © 2004. John Wiley & Sons Limited.)

Calendar years analysed	Statins					
	lovastatin 1988–2001	pravastatin 1992–2001	simvastatin 1992–2001	fluvastatin 1994–2001	atorvastatin 1997–2001	cerivastatin 1998–2001
All cases						
Cases	180	19	136	1	51	479
No. of prescriptions (000s)[b]	99 485	83 673	120 188	38 119	149 706	11 172
Crude reporting rate, cases/100 000 prescriptions	0.18	0.02	0.11	0.00	0.03	4.29
Monotherapy						
Cases	120	17	99	1	45	200
Estimated no. of prescriptions (000s)[c]	97 336	82 000	118 986	37 791	147 610	11 038
Crude reporting rate, cases/100 000 prescriptions	0.12	0.02	0.08	0.00	0.03	1.81
Combination with gemfibrozil[d]						
Cases	60	2	37	0	6	279
Estimated prescriptions (000s)[b]	2109	1422	962	316	1198	22
Crude reporting rate, cases/100 000 prescriptions	2.84	0.14	3.85	0.00	0.50	1248.66

a Cases identified in the Adverse Events Reporting System database with a creatine kinase level of >10 000 IU/L, signs and symptoms (myalgia, myopathy, gait disturbance) and clinical diagnosis of rhabdomyolysis.

b All dispensed prescriptions for all years the drug was marketed between 1988 and July 2001 (IMS Health NPA Plus™, excluding long-term care).

c Estimate of prescriptions for all statin therapy, with or without concomitant gemfibrozil therapy, based on percentage of mentions (IMS Health NDTI™) summed across all years of marketing for each drug and applied to prescriptions for all years each drug was marketed (IMS Health NPA Plus™).

d This analysis does not include concomitant therapy with fenofibrate, which was prevalent in 0–1% of reports across statins, or clofibrate, which occurred only in 0.04% of lovastatin reports. Few cases of rhabdomyolysis were reported for any statin plus fenofibrate or clofibrate; they are not included in this analysis.

Why might gemfibrozil be more susceptible than fenofibrate to myopathy when combined with statins? Work by Prueksaritanont et al.[52,124] suggests that glucuronidation is a pathway for the elimination of the active hydroxyl acid metabolites of statins including cerivastatin, atorvastatin, lovastatin and simvastatin. Gemfibrozil appears to inhibit this statin glucuronidation, which results in elevated statin serum levels. Fenofibrate, on the other hand, appears to have a significantly less inhibitory effect on statin glucuronidation, and this might help explain the difference between fibrates in their ability to affect the pharmacokinetics of statins. Of note, gemfibrozil had the greatest inhibitory effect on cerivastatin glucuronidation, which might explain the very high rates of rhabdomyolysis seen when cerivastatin is combined with gemfibrozil.

Although both gemfibrozil and fluvastatin are weak CYP2C9 substrates,[125] gemfibrozil has minimal effects on fluvastatin plasma concentrations or systemic exposure, and no patients in a small crossover study experienced myopathy or rhabdomyolysis during 2 weeks of treatment with fluvastatin 20mg together with gemfibrozil 600mg.[126-129] In contrast, 5% of patients receiving pravastatin together with gemfibrozil experienced muscular problems requiring study drug withdrawal.[130] Gemfibrozil also more than doubled the systemic exposure of simvastatin and substantially increased concentrations of both pravastatin and rosuvastatin in single-dose and multiple-dose pharmacokinetic studies.[126,127,129]

As reported by Davidson,[131] on statin/fibrate combination therapy, simvastatin, pravastatin and rosuvastatin are associated with a 2-fold increase in the C_{max} of gemfibrozil, with no pharmacokinetic interactions when these agents are used in combination with fenofibrate. Cerivastatin and lovastatin result in a 2.3- and 2.8-fold increase in C_{max}, respectively, combined with gemfibrozil. Data are not available for the combination of lovastatin and fenofibrate, but there is no effect with the cerivastatin/fenofibrate combination. With atorvastatin, there is an expected increase in C_{max}, with no effect in combination with fenofibrate. Fluvastatin has no pharmacokinetic interaction with either fibrate. A summary of significant statin/fibrate pharmacokinetic interactions appears in table V.

Table V. HMG-CoA reductase inhibitor (statin)/fibrate combination therapy: pharmacokinetic interactions

Statin	Gemfibrozil	Fenofibrate
Atorvastatin	↑ in C_{max}	No effect
Simvastatin	↑ in C_{max}	No effect
Pravastatin	↑ in C_{max}	No effect
Rosuvastatin	↑ in C_{max}	No effect
Fluvastatin	No effect	No effect
Lovastatin	↑ in C_{max}	Not available
Cerivastatin	↑ in C_{max}	No effect

C_{max} = maximum concentration; ↑ indicates increase.

4.3 Other Adjunctive Treatments

Combinations of statins with nicotinic acid and/or bile acid resins (sequestrants) have been evaluated in a number of chiefly middle-aged patient populations, though not specifically in elderly individuals. Representative data are reported in the following sections.

4.4 Statins/Nicotinic Acid (Niacin)

The HATS (HDL-Atherosclerosis Treatment Study) trial showed that CHD patients with low HDL-C and average LDL-C levels derived marked clinical and angiographic benefits from treatment with simvastatin plus nicotinic acid.[132] In this 3-year, double-blind, placebo-controlled trial, 80 patients were randomised to simvastatin at a starting dose of 10mg in patients with LDL-C values of ≤110 mg/dL, and 20mg in those with LDL-C levels of >110 mg/dL. Simvastatin doses were increased as necessary to maintain LDL-C levels between 40 and 90 mg/dL. Slow-release nicotinic acid was increased from 250 to 1000mg twice daily and crystalline nicotinic acid was added and titrated to a dose of up to 4 g/day in order to reach present HDL-C targets. The placebo group in the HATS study was not a true control group in that simvastatin was administered to any patient with an LDL-C value of >140 mg/dL and a small dose of nicotinic acid (50mg) known to elicit flushing but not affect lipid levels was included in the nicotinic acid/placebo arm.

In a safety/tolerability analysis involving 160 patients with a mean age of approximately 53 years, no patient receiving simvastatin/nicotinic acid had consecutive elevations of transaminase levels to ≥3×ULN or any creatine kinase level elevation to

≥5×ULN. Adverse events possibly related to simvastatin and/or nicotinic acid included gastrointestinal symptoms, nausea, cutaneous effects (itchy/dry skin, rash), muscle aches and flushing (chiefly mild or moderate). Although severe flushing was more frequent in patients receiving simvastatin/nicotinic acid (5%) compared with placebo (0%; p = 0.060), 91% of patients receiving simvastatin/nicotinic acid rated it as very or fairly easy to take, compared with 86% of the placebo group (p = NS).[133] One concern with high-dose nicotinic acid is altered glucose disposal. Although glycaemic control was variable and slightly worse in the simvastatin/nicotinic acid group compared with the placebo group during the first few treatment months, glycaemic control reverted to pretreatment levels and stabilised thereafter. New cases of diabetes and new patients with impaired fasting glucose levels were more frequent in the simvastatin/nicotinic acid group compared with the placebo control group, but this difference was not statistically significant.[133]

In an open-label study involving 814 adults (mean age = 59 years) treated with extended-release nicotinic acid plus lovastatin at doses of 0.5g/10mg to 2.0g/40mg, the adjunctive treatment was well tolerated, although 10% of patients discontinued treatment because of flushing.[134] Other cutaneous effects included pruritus (16%) and rash (9%), and 24% of patients experienced gastrointestinal adverse events. There were no cases of myopathy or rhabdomyolysis; however, seven (0.9%) patients discontinued treatment because of raised creatine kinase levels. Two patients with >10-fold creatine kinase level elevations had undergone strenuous exercise or experienced trauma.[134]

Fluvastatin/nicotinic acid was well tolerated in a short-term study involving 74 patients with LDL-C levels of ≥160 mg/dL (mean age = 54.1 years). Patients were randomised to fluvastatin 20mg or placebo for 6 weeks, then crystalline nicotinic acid was added to both treatment arms at a dose of 0.1g titrated to a maximum tolerated dosage of 3g daily from weeks 8 through 15. Among 57 patients completing treatment week 15, the most frequent adverse event was flushing, which occurred in 60.5% of patients receiving fluvastatin/nicotinic acid and 44.4% of those receiving nicotinic acid/placebo. Other adverse events included pruritus in 26.3% of fluvastatin/nicotinic acid patients. Cutaneous effects, including flushing, contributed to four of 17 discontinuations resulting from adverse events, and muscle aches contributed to two discontinuations. However, there were no cases of myopathy or rhabdomyolysis, and none of the discontinuations related to adverse events were conclusively attributed to fluvastatin/nicotinic acid therapy.[135]

The National Institutes of Health has recently funded an ongoing study evaluating the effects on a composite cardiovascular outcome of simvastatin/extended-release nicotinic acid compared with statin monotherapy in patients with established vascular disease and atherogenic dyslipidaemia (including metabolic syndrome): the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides and Impact on Global Health Outcomes) trial.

4.5 Statins/Resins

In HARP (the Harvard Atherosclerosis Reversibility Project), a total of 91 patients aged up to 75 years with angiographically documented stenosis, a total cholesterol level of 180–250 mg/dL and a ratio of total cholesterol to HDL-C level of >4.0 were randomised to usual or stepped care involving pravastatin, nicotinic acid, the bile acid resin colestyramine, or gemfibrozil for up to 2.5 years. Most adverse events were attributed to either nicotinic acid or colestyramine.[136] No patient had myopathy or rhabdomyolysis or a confirmed elevation of any serum liver enzyme level to >3×ULN while receiving study medication. Two patients experienced decreased serum thyroxine levels (<0.8 × lower limit of normal) during treatment with nicotinic acid 2.25–3g daily, and another two patients (with diabetes mellitus) had blood glucose level elevations (to 1.5×ULN), which led to dose reduction or discontinuation.[136]

The chief adverse events included gastrointestinal symptoms in 59% of patients in the stepped-care treatment group compared with 6% of those randomised to usual care. When colestyramine 4–24 g/day was added to pravastatin/nicotinic acid regimens in 21 patients, seven (33%) reported new gastrointestinal symptoms and 11 (52%) discontinued therapy.[136] Constipation and the need to separate resin from statin administration to avoid

changes in statin absorption limit the use of bile acid resins in elderly patients, particularly those receiving polypharmacy. On the other hand, resins are of potential value in patients receiving multiple medications because the sequestrants are nonsystemic.

5. Conclusions

In summary, the vast majority of CHD deaths in Americans occur in persons aged ≥65 years. The proportion of atherosclerotic burden shouldered by elderly patients is likely to increase with the advancing median population age and life expectancy of Western societies. Although more deaths and other coronary events can be averted via treatment of hypercholesterolaemia in elderly patients compared with their younger counterparts, many, if not most, elderly patients at risk for CHD do not receive treatment with a statin. Given ongoing demographic trends, further randomised controlled trials evaluating the efficacy and safety of statins in preventing heart disease and stroke exclusively among elderly patients, including larger numbers of octogenarians, are warranted. This is particularly important in primary prevention.

At present, randomised controlled trials involving >10 000 patients show that elderly individuals at increased cardiovascular risk derive equivalent and often more effective care from statin therapy than younger patients, without any discernible excesses in adverse events. Although advancing age is a risk factor for myopathy, it is reassuring that low rates of fatal rhabdomyolysis have been reported in most statin clinical trials and in current pharmacoepidemiological surveillance programs. With increasing obesity, metabolic syndrome, diabetes and CKD in the elderly, combination lipid-lowering therapies will be used more frequently with resultant increases in adverse events. Of the current statins, it appears that fluvastatin has the least myopathic potential when combined with the fibrates, particularly gemfibrozil, and may be the statin of choice in elderly patients with mixed dyslipidaemia requiring combination therapy. Finally, given the large number of elderly patients treated successfully and safely in the major statin trials such as the Heart Protection Study, the data in aggregate should help clinicians overcome the 'age gap' in statin prescribing.

Acknowledgements

Dr Jacobson has served as a consultant for AstraZeneca, Bristol-Myers Squibb, Kos, Merck, Novartis, Pfizer, Reliant, and Schering-Plough. Assistance in manuscript preparation was provided by Stephen W. Gutkin, Rete Biomedical Communications Corp. (Ridgewood, NJ). Dr Jacobson received partial funding for this manuscript from an unrestricted educational grant from Reliant Pharmaceuticals, Liberty Corner, New Jersey, USA.

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