Balancing Efficacy and Tolerability Issues with Statin Therapy—Considerations for the Use of Pitavastatin in Special Patient Populations

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Abstract

One of the main objectives of cardiovascular care is to control elevated low-density lipoprotein cholesterol (LDL-C). Statins are the mainstay for managing LDL-C with proven high efficacy and satisfactory safety profiles. However, the most known side effects are muscle symptoms, which are particularly common in individuals who often have co-existing conditions and are taking multiple medications. The latest statin that has become available, pitavastatin, is not known to cause cytochrome P450-mediated drug–drug interactions, making it an ideal statin for individuals at a high risk for side effects. Pitavastatin will be particularly beneficial in treating patients with mixed dyslipidemia, as it is effective in reducing triglycerides and increasing high-density lipoprotein cholesterol (HDL-C). Pitavastatin has an established history of use, and has a safety and adverse event profile similar to that of other existing statins. Individuals at high risk from side effects with statins include older people (>65 years), individuals with diabetes, kidney disease, or metabolic syndrome and individuals taking multiple medications. South Asian populations that have migrated to Western countries are at particularly high risk for cardiovascular disease, and this population also has an increased risk for statin-related side effects. This article will summarize the factors that place individuals at high risk for dyslipidemia, treatment of high risk populations with statins, and the issues associated with treating high risk populations with statins. The benefits of treating these individuals with pitavastatin will be reviewed, as well as alternative forms of therapy.

Keywords

Cardiovascular disease (CVD), coronary heart disease (CHD), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), dyslipidemia, hypercholesterolemia, statin, tolerability, elderly, diabetes, chronic kidney disease (CKD), metabolic syndrome, red yeast rice, omega-3 fatty acid, co-enzyme Q10

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Cardiovascular disease (CVD) is the number one cause of death globally and was the leading cause of death in both men and women ≥65 years of age in the US in 2007.[1,2] In 2004 alone, an estimated 17.1 million people died from CVD, representing approximately 29 % of deaths worldwide.[2] Of these deaths, an estimated 7.2 million were due to coronary heart disease (CHD) and 5.7 million were due to stroke.[2] In the year 2030, it is estimated that 23.6 million individuals will die from CVD.[2] Furthermore, the greatest increase in the number of deaths due to CVD will occur in South-East Asia.[2] Consequently, CVD is a public health issue of growing global concern.

Though CVD is a multifactorial disease, elevated low-density lipoprotein cholesterol (LDL-C) is a major risk factor for CVD, particularly in older individuals (≥65 years of age).[3] Mixed dyslipidemia presents as low levels of high-density lipoprotein cholesterol (HDL-C), elevated triglycerides (TG), elevated apolipoprotein B (apoB) and elevated levels of small, dense LDL, and is associated with type 2 diabetes.[4] Each lipid abnormality is associated with CVD risk, which is independent of LDL-C levels.[5] Furthermore, CVD risk is increased in patients who exhibit both elevated TG and low HDL-C.[5] This population is characterized by increased levels of apoB, although LDL-C may also be increased, borderline, or normal.[6]

Risk Factors for Dyslipidemia

Age

Age alone places individuals at increased risk for CVD, independently of other risk factors.[1] CVD is the leading cause of morbidity and mortality in the elderly, with the highest incidence and prevalence in individuals aged ≥65 years.[1,7,8] The cumulative risk for CVD also increases sharply between 60 and 90 years of age, as demonstrated by the Framingham

Heart Study,[7] and mortality rates are highest in the population >65 years of age,[9] with CVD being the leading cause of mortality in the US in 2004, responsible for over 29 % of deaths in individuals in this age group that year.[8] An estimated 23.6 million people will die from CVD-related causes during 2030 and these are projected to remain the single leading causes of mortality.[2] Thus, since the elderly population has more than doubled over the last 50 years and continues to increase, this will result in a higher incidence of CVD in the future.[10]

Most, but not all studies demonstrate that elevated total serum cholesterol is a risk factor for CVD in the older populations (Rotterdam study and the Systolic hypertension in the elderly program [SHEP]).[11–18] In addition, high LDL-C and low HDL-C are associated with CVD risk in this population, as demonstrated by the Framingham heart study and SHEP.[12,15]

Diabetes

Diabetes, particularly type 2 diabetes, is an increasingly prevalent global disease that is expected to affect 5.4 % of the worldwide adult population by the year 2025, an increase of 1.4% from 1995.[19] This is expected to rise in the US to 7.2 % by 2050.[20] Risk factors for type 2 diabetes include increased age, obesity and lack of physical activity.[21] Type 2 diabetes has serious ramifications, including an association with cardiovascular risk factors, with its highly atherogenic dyslipidemia.[22] Patients with diabetes are considered a CHD risk equivalent, as described in the third report issued by National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (NCEP-ATP III) report.[23] Specifically, the risk for developing CHD is increased two- to eight-fold in individuals with type 2 diabetes and CHD accounts for 80 % of all mortality in this patient population.[24,25]

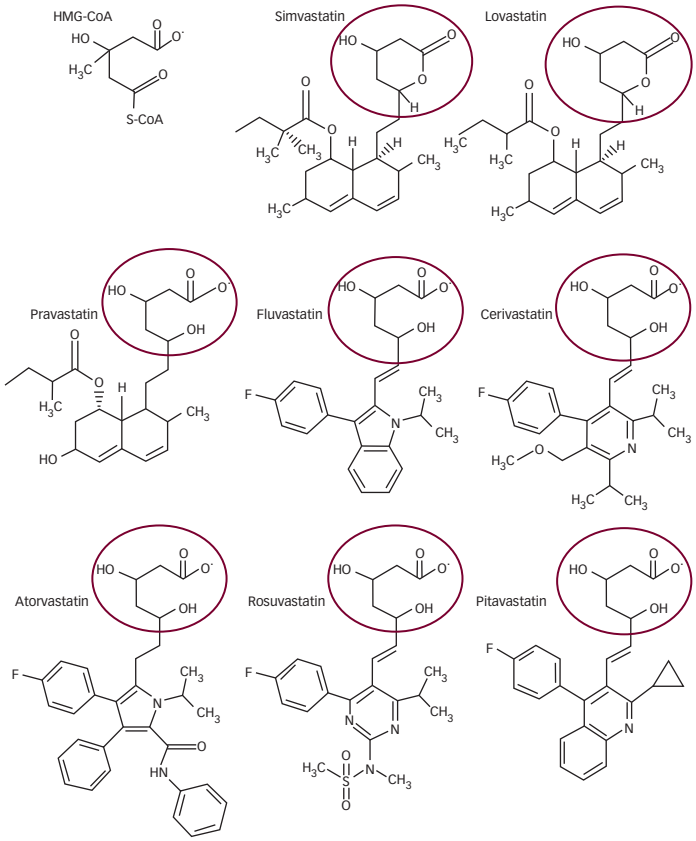
Dyslipidemia is one of the major risk factors for CHD in diabetes.[26] Diabetic dyslipidemia is characterized by high TG, low HDL-C and increased small, dense LDL.[27–31] The dyslipidemia is only partially corrected by control of the hyperglycemia, abnormalities persist, partly due to the effects of insulin resistance on lipoprotein metabolism.[28,29]

Insulin resistance is a risk factor for diabetes.[32] Insulin resistance is confounded by other risk factors including central obesity, hyperglycemia, hypertriglyceridemia, low HDL, and hypertension.[33] The CHD and atherothrombotic risk factors that accompany insulin resistance syndrome are linked with the onset of diabetes and are also associated with adverse cardiovascular effects.[34,35]

Kidney Disease

Chronic renal insufficiency is characterized by specific abnormalities in lipoprotein metabolism, affecting both apolipoprotein A and B-containing lipoproteins.[36] This lipid profile markedly increases the risk for CVD, and it is believed that dyslipidemia is also a significant risk factor for the progression of renal insufficiency in chronic renal disease.[37,38] There is also evidence to suggest that individuals in the very initial stages of kidney disease, which manifests as microalbuminuria, develop CVD.[38] There is mounting evidence for an association between kidney dysfunction and multiple risk factors for CVD, including dyslipidemia. Furthermore, CVD risk factors such as dyslipidemia, may cause kidney damage in the form of increased serum creatinine or proteinuria, as well as injury to the vasculature.[39–42] However, the role of dyslipidemia in chronic kidney disease (CKD) can only be confirmed by randomized, controlled, interventional trials and the trials to date have had insufficient statistical power to test the hypotheses.[38] Correction of lipid abnormalities associated with renal disease slows the progression of chronic renal failure.[43,44] Furthermore, it is likely that direct treatment of hyperlipidemia with statins could reduce the high incidence of CVD in patients with CKD.[38] A recent study has confirmed this.[45]

Figure 1: Pitavastatin and Other Statins with the Moiety Similar to HMG-CoA Highlighted

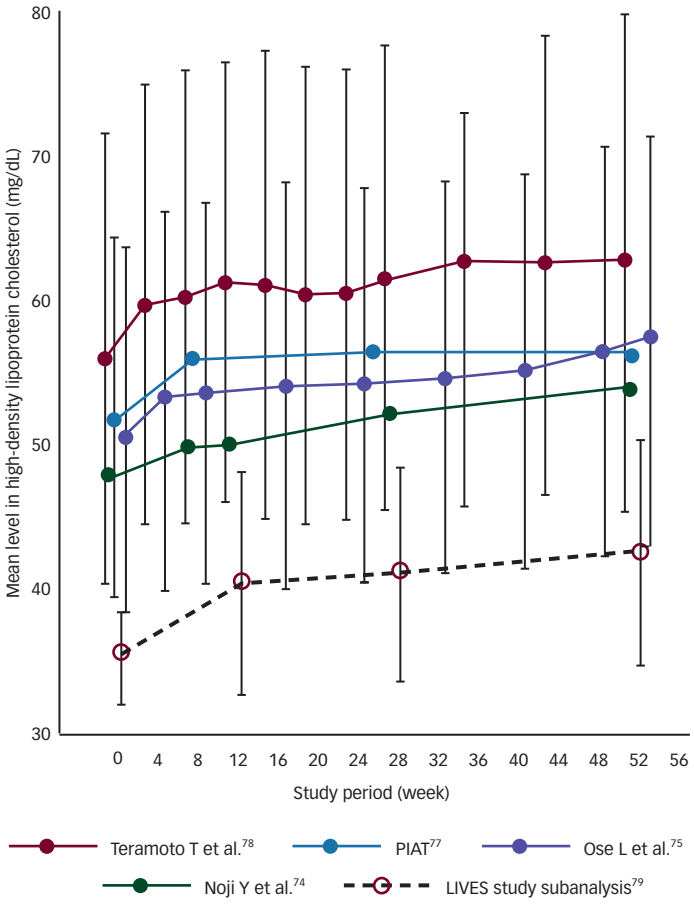


Adapted from Ose L, Clin Lipidol, *2010.*[144]

Metabolic Syndrome

Metabolic syndrome describes a group of atherosclerotic CVD risk factors including visceral obesity, insulin resistance, dyslipidemia, hypertension, and pro-inflammatory/thrombotic state.[46,47] More than one-quarter of the US adult population over 50 years of age suffers from metabolic syndrome, and the actual prevalence of metabolic syndrome is between 24.6 and 30.9 % in Europe.[48,49] Epidemiological studies have shown that individuals with metabolic syndrome are at three to five times' higher risk for diabetes and/or CVD, as well as significantly increased risk for cardiovascular mortality.[47–50] Obesity has caused marked increases in both diabetes and metabolic syndrome in the US, which will ultimately result in exponential increase in CVD.[51] The Framingham heart study recently showed that the prevalence of metabolic syndrome doubled after 10 years of follow-up from 23.5 to 40.6 %.[52] The National Cholesterol Education Program (NCEP) Adult Treatment Panel III identified metabolic syndrome as a secondary target of therapy for management of CVD beyond cholesterol-lowering.[53]

Figure 2: Time Course Of High-Density Lipoprotein Cholesterol Levels In Long-Term Clinical Studies Of Pitavastatin



Note: Data are expressed as mean ± standard deviation. Teramoto et al., 2009[79] is subanalysis for patients whose baseline high-density lipoprotein cholesterol was <40 mg/dL. Adapted from Sasaki J, 2010.[73]

Treatment of Dyslipidemia with Statin Therapy

A major advance in the treatment of hyperlipidemia was the development of statins, which were initially derived from natural sources (fungi) and later, synthetically.[9,54] A total of seven statins are currently available. Natural statins include pravastatin, lovastatin, and simvastatin; synthetic statins include fluvastatin, atorvastatin, rosuvastatin, and, more recently, pitavastatin. Statins differ in their hydrophilic properties, bioavailability, clearance (see *Figure 1*), their LDL-C-lowering abilities and their drug interaction profiles.[9,55] These factors are considered to be most important when treating an older population,[9] and other populations at a high risk for drug–drug interactions.

Statins have shown average risk reductions of 27 and 15 % for major coronary events and all-cause mortality, respectively.[56] They exert their LDL-C-lowering effect primarily through very selective inhibition of the HMG-CoA-reductase enzyme, which mediates the first committed step in the mevalonate pathway of cholesterol biosynthesis.[57,58] The most commonly used statins in the US, atorvastatin and simvastatin, are metabolized by the cytochrome P450 (CYP) 3A4 isoform,[59] whereas pitavastatin,[60] rosuvastatin, fluvastatin and pravastatin are not dependent on CYP 3A4.[61]

Pitavastatin, the newest of the statins, has a cyclopropyl group side chain as part of its molecular structure highly potent.[62] This unique cyclopropyl group is thought to reduce the activity of the HMG-CoA-reductase enzyme by a factor of five, and to significantly increase the transcription and activity of LDL receptors.[62,63] Importantly, pitavastatin is minimally metabolized and is not a substrate of the CYP 3A4 isoenzyme. Rather, the principle route of metabolism for pitavastatin is via glucuronidation, with only very marginal metabolism via CYP 2C9, and to a lesser extent, CYP 2C8.[64,65] This is important because approximately 75 % of all drugs metabolized require the CYP system as their principle route of metabolism and nearly 50 % of these agents utilize the CYP3A pathway.[66] As many patients are on a number of concomitant medications, based on its metabolism, pitavastatin may bypass any potential for CYP-mediated drug–drug interactions. Compared with atorvastatin, pitavastatin does not lower co-enzyme Q10 (CoQ10), which is an essential cofactor in the mitochondrial electron transport chain.[67] The intracellular depletion of CoQ10 due to statins, at least in part may be a potential cause of myositis in humans.[67] Clinical trials have shown that pitavastatin is comparable to atorvastatin and simvastatin in improving lipid measures,[68–71] but is more potent than pravastatin as observed in short-term, phase III trials where pitavastatin demonstrated significantly greater LDL-C reductions than pravastatin across three pair-wise dose comparisons (1 versus 10 mg, 2 versus 20 mg, and 4 versus 40 mg) over 12 weeks.[69,72,73] Pitavastatin is effective in reducing TG and several non-randomized trials that studied the effects of long-term administration of pitavastatin reported a sustained increase in HDL-C levels with pitavastatin treatment (see *Figure 2*),[73–79] and it is therefore particularly beneficial for treatment of patients with mixed dyslipidemia. Pitavastatin has shown a significant effect to increase HDL-C even after switching from other cholesterol-lowering drugs (see *Figure 3*).[79] It has a similar safety and adverse event profile to other statins.[72,73] Pitavastatin was first developed and launched in Japan in 2003.[73] Its safety and efficacy was established in Japan by the Livalo effectiveness and safety (LIVES) study, which was a post-marketing study conducted in over 20,000 patients with a two-year follow-up for each patient since 2003.[80] Pitavastatin was approved in South Korea in 2005, and subsequently in Thailand (2007) and China (2008). In June 2010, pitavastatin was launched in the US, following approval by the Food and Drug Administration (FDA) in August of 2009. In July 2010, pitavastatin was approved in the EU and launch continues across various European countries.

Statin Therapy in Special Populations

The Elderly

Initially excluded from statin trials, the very elderly (i.e. ≥70 years of age) may experience similar cardiovascular benefits with statins as younger patients.[81,82] The Prospective study of pravastatin in the elderly risk (PROSPER) trial was a randomized, controlled trial that focused on CHD risk in those between 70 and 82 years of age.[83] Individuals were enrolled if they had pre-existing vascular disease (coronary, cerebral, or peripheral) or if they were at increased risk for CVD due to smoking, hypertension, or diabetes. Study participants were assigned to pravastatin (40 mg/day) or placebo. Pravastatin (compared with placebo) reduced LDL-C by 34 % and induced a significant reduction in both the primary composite endpoint of CHD death, nonfatal myocardial infarction (MI), and stroke (15 %, p=0.014), and in the secondary endpoint of CHD death or non-fatal MI (19 %, p=0.006).[83]

The Study assessing goals in the elderly (SAGE) also focused on CHD risk reduction in the elderly, in which coronary risk reduction was examined subsequent to intensive lipid lowering with atorvastatin versus moderate therapy with other statins.[84] It was an international (conducted in 16 countries), multicenter, prospective, randomized, double-blinded study in which atorvastatin (80 mg/day) or pravastatin (40 mg/day) were administered to study participants who were between 65 and 85 years of age. Treatment with both atorvastatin and pravastatin resulted in significant (p<0.001) reductions in the total duration of myocardial ischemia, although the difference in the reductions between the study groups was not significant. The SAGE trial affirmed that cholesterol management with a statin should be considered in higher-risk elderly patients.[85]

Despite the evidence for the cholesterol-lowering benefits of statins in older adults, they continue to be underused in this population, mainly due to poor physician awareness and patient adherence to this type of medication.[9]

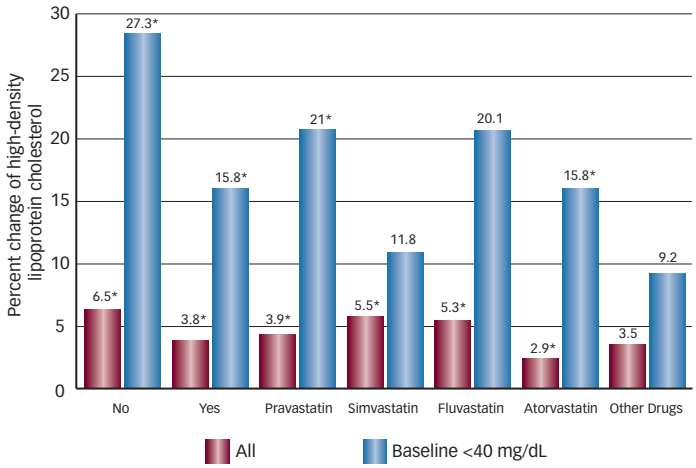
Patients with Diabetes

Multiple agents are often used to treat patients with diabetes in order to achieve therapeutic goals.[26] Severe hypertriglyceridemia in patients with diabetes can be managed with fat restriction, optimal glucose control with intravenous insulin if necessary, fibrates, omega-3 fatty acids, and/or niacin therapy to prevent pancreatitis. However, statins are the drug of choice for treatment of typical diabetic dyslipidemia, with mild to moderate hypertriglyceridemia in individuals with diabetes.[86] Rosuvastatin has been shown to have consistent efficacy across patient subgroups defined by age >65 years, female sex, post-menopausal status, hypertension, atherosclerosis, type 2 diabetes, and obesity.[87] Furthermore, the findings of the Heart protection study (HPS)[88] and the Collaborative atorvastatin diabetes study (CARDS)[89] contributed to changing American Diabetes Association (ADA) guidelines for primary prevention of CVD in diabetes, such that all patients with diabetes over the age of 40 years are now considered for statin therapy regardless of baseline LDL.[90]

Meta-analysis of the Long-term intervention with pravastatin in ischemic disease (LIPID), the Cholesterol and recurrent events (CARE), and the Scandinavian simvastatin survival study (4S) trials demonstrated a 28 % reduction in coronary events and 32 % reduction in stroke in patients with diabetes on statin treatment.[91] Furthermore, the effect of statins was greater in patients with diabetes than patients without diabetes.[91] Meta-analysis by the Cholesterol treatment trialists' (CTT) collaboration suggested that the greater the LDL-C-lowering, the greater the benefit.[92] There was a 21 % reduction (p<0.0001) in major vascular events per mmol/l reduction in LDL-C in patients with diabetes, which was almost identical to that seen in patients without diabetes.[92]

A significant reduction in LDL-C was observed in patients with type 2 diabetes treated with a combination of simvastatin and ezetimibe compared with treatment with atorvastatin (p<0.001) in the Vytorin versus atorvastatin in patients with type 2 diabetes mellitus and hypercholesterolemia (VYTAL) study. Additionally, simvastatin plus ezetimibe was more effective at achieving an LDL-C level of <70 mg/dl, improving HDL-C, and non-HDL-C levels (p<0.001) and TG and residual non-lipid risk factors (p<0.02).[93] Therefore, simvastatin and ezetimibe could be an effective combination in clinical practice.[94]

Figure 3: Effect Of Pitavastatin On High-density Lipoprotein Cholesterol After Switching From Other Cholesterol-lowering Drugs



Bar chart depicts the incremental change in high-density lipoprotein cholesterol (HDL-C) following switch to pitavastatin from prior statin or other lipid lowering agents for all patients with any pre-treatment HDL-C level compared with the subset of patients with HDL-C levels still <40 mg/dl at the time of switch to pitavastatin.
No— All patients who did not receive pre-treatment lipid lowering medication (treatment naive patients)
Yes— All patients switched to pitavastatin from all other lipid modifying therapy
**p<0.01 (versus baseline).*
Adapted from Teramoto T, et al., 2009.[79]

The Action to control cardiovascular risk in diabetes (ACCORD) trial was conducted to investigate indications for combination therapy with statins, including simvastatin, and other lipid-lowering agents, including fibrates, for patients with type 2 diabetes.[95–97] For this trial, the effect of fenofibrate, dosed according to baseline GFR, on simvastatin therapy (20–40 mg) was measured in approximately 5,518 subjects with a mean age of 62 years and a history of CVD. The primary endpoint measured was a composite of cardiovascular death, non-fatal MI, and non-fatal stroke. No significant effects of fenofibrate on primary (hazard ratio [HR] 0.92; 95 % confidence interval [CI] 0.79–1.08; p=0.32) or secondary (individual components of primary composite including revascularization and hospitalization for heart failure and total mortality) outcomes were observed over the 4.7-year follow-up period. Combination therapy of simvastatin with fenofibrate was considered safe and no major differences were observed in serious adverse events between the two treatment groups. The mean level of serum creatinine increased and a significant reduction in microalbuminuria and macroalbuminuria was observed, with no difference in the occurrence of end-stage renal disease (ESRD).[97]

The ADA standards of care for diabetes state that statin therapy should be initiated in individuals with diabetes and other cardiovascular risk factors with a target LDL-C of 100 mg/dl. Furthermore, a target LDL-C of 70 mg/dl is an option in patients with diabetes and CVD.[98] For the highest risk patients it would be desirable to treat to a non-HDL-C target <100 mg/dl and an apoB target <80 mg/dl.[99]

Kidney Disease

Although the benefits of statin treatment have been proven in CVD and diabetes, there is uncertainty as to the effectiveness of statins in

patients with advanced CKD,[100] but statins have been shown to be an effective treatment in the initial stages of CKD. The Deutsche diabetes dialyse studie (4D Study) was a prospective, randomized, double-blinded study conducted in 178 dialysis centers across Germany over four years between March 1998 and October 2002, in which patients between 30 and 83 years of age with type 2 diabetes were randomized to either atorvastatin 20 mg or placebo.[101] The primary end-point was a composite of death from cardiac causes, non-fatal MI, and stroke. Secondary endpoints included death from all causes and all cardiac and cerebrovascular events combined. Atorvastatin did not have a significant effect on the individual components of the primary endpoint, except that the relative risk (RR) for fatal stroke among those receiving the drug was 2.03 (95 % CI 1.05–3.93; p=0.04). Atorvastatin reduced the rate of all cardiac events combined (RR 0.82; 95 % CI 0.68–0.99; p=0.03) but not all cerebrovascular events combined (RR 1.12; 95 % CI 0.81–1.55; p=0.49) or total mortality (RR 0.93; 95 % CI 0.79–1.08; p=0.33). Atorvastatin did not have a statistically significant effect on the composite primary endpoint of cardiovascular death, non-fatal MI, and stroke in ESRD patients with diabetes receiving hemodialysis.[102]

A recent study investigated the relationship between CKD and CVD and retrospectively evaluated the effect of low doses (10–20 mg) of pravastatin on prevention of CVD and renal function in 7,196 Japanese patients with hypercholesterolemia and normal kidney function, mild CKD or moderate CKD who had been enrolled in the Management of elevated cholesterol in the primary prevention group of adult Japanese (MEGA) study.[103] However, patients with severe kidney disease were excluded from the study since they are not treated with statins according to Japanese guidelines. Patients with moderate CKD had 35–49 % higher incidence of CVD events compared with patients with either normal kidney function or mild CKD. In this study, pravastatin significantly reduced CHD by 48 % (p=0.02), stroke by 73 % (p<0.01), CVD by 55 % (p<0.01) and total mortality by 51 % (p=0.02). Furthermore, the increase in estimated glomerular filtration rate (eGFR) in patients with moderate CKD on a regimen of pravastatin and diet was significantly higher (+6.3 %; p=0.03) than in patients on diet alone (+5.1 %).

Following the previous study by Nakamura et al., a study was conducted in uninephrectomized male Wistar rats to investigate the effect of pitavastatin and/or spironolactone on streptozoticin-induced diabetes.[104] Pitavastatin ameliorated proteinuria, normalized creatinine clearance, serum creatinine, and blood urea nitrogen levels and attenuated the deposition of glomerular collagen. Renal expression of messenger RNA (mRNA) for angiotensin-converting enzyme (ACE) and CYP11B2 mRNA, aldosterone synthase, and the amount of aldosterone in the kidney was also suppressed by pitavastatin. The renoprotective effects of pitavastatin against diabetic nephropathy observed in the animals suggest a potential indication for pitavastatin treatment in patients with diabetes-related kidney disease.

To that end, the LIVALO effectiveness and safety (LIVES) study was a large-scale, long-term, prospective post-marketing surveillance study of hypercholesterolemic patients treated with pitavastatin, a subset of which was used to evaluate the effects of pitavastatin on eGFR.[105] A significant increase (+5.4 ml/minute/1.73 m^2; p<0.001) in eGFR was observed after 104 weeks of treatment with pitavastatin, suggesting a possible beneficial effect of this statin on CKD.[105]

Collectively, the effects of statins on kidney disease observed in studies to date shows promise for this type of therapy in this patient population.

Metabolic Syndrome

Dyslipidemia in patients with metabolic syndrome, as in type 2 diabetes, has a distinctive profile. It is characterized by hypertriglyceridemia and excessive postprandial lipemia, low HDL-C concentrations and high small LDL particles, which are relatively cholesterol poor, which all contribute significantly to patients' CVD risk.[106] The ApoB level is a proxy for several atherogenic particles as each atherogenic lipoprotein particle contains one ApoB.[107] Even though LDL-C level frequently does not increase, ApoB and ApoB/ApoA-I ratio does increase. Thus it is likely that therapy must be tailored to target the key features of lowered HDL-C and raised TG; this is in addition to lowering ApoB-containing lipoproteins, other than and including LDL.[108] Women with diabetes have larger increases in LDL-C and decreases in HDL-C than men with diabetes and individuals who are not diabetic; increases in remnant particle cholesterol and TG are also greater in the former population compared to the latter population. The situation is similar for patients with metabolic syndrome.[108]

Although treatment strategies have greatly improved outcomes for CVD, the increase in the incidences of diabetes and metabolic syndrome, particularly in the US, threaten to undermine these achievements. The metabolic syndrome and diabetes pose a large health-economic burden, costing the US $174 billion in 2007.[109] However, several clinical trials have shown that statins reduce cardiovascular events in individuals with metabolic syndrome and type 2 diabetes, suggesting that statins are effective in treating these diseases.[88,92,110–115]

It has been demonstrated that the benefits of statins for the treatment of metabolic syndrome are at least comparable, if not greater, than for patients without metabolic syndrome.[108] The 4S study demonstrated a 46 % reduction in total mortality and a 61 % reduction in coronary mortality in metabolic syndrome patients on simvastatin treatment, compared with 28 and 38 % risk reduction, respectively, in individuals who were not on statin treatment. However, the differences in risk reduction between treated and non-treated groups were not significant.

In the Treating-to-new-targets (TNT) trial, a higher-dose statin (80 mg atorvastatin, daily) decreased the relative risk for CVD by 20–30 % compared with a lower dose of statin (10 mg atorvastatin, daily) in patients with coronary disease and type 2 diabetes or with metabolic syndrome without diabetes.[113] However, in the Comparative study with rosuvastatin in subjects with metabolic syndrome (COMETS) trial, rosuvastatin had a significantly greater effect than atorvastatin in lowering LDL-C (p<0.001), as well as improving the lipid profile in metabolic syndrome patients.[116]

Despite the studies conducted to date on the effects of statins on metabolic syndrome, no general consensus on treatment of these patients has been reached. Treatment regimens remain somewhat inadequate, and better guidelines are needed in order to achieve effective treatment for dyslipidemia in patients with diabetes and metabolic syndrome.[108]

South Asian Population Living in the West

South Asians have the highest prevalence of CHD compared with all ethnic groups, the greater proportion of disease risk factors occurring

Table 1: Efficacy and Safety Profile of Statins

Statin (Type)	Licensed Dosing Range (% LDL-C Reduction)*	Metabolism of Statin	Major Drug Metabolic Interactions Increasing Risk for Myopathy
Lovastatin (natural)	20–80 mg daily (30 % with 40 mg)	Mainly CYP3A4	Potent inhibitor of CYP3A4
Pravastatin (natural)	20–80 mg daily (34 % with 40 mg)	Sulfation, biliary and urinary excretion	
Simvastatin (natural)	10–80 mg (41 % with 40 mg)	Mainly CYP3A4	Potent inhibitor of CYP3A4
Atorvastatin (synthetic)	10–80 mg daily (38 % with 10 mg)	CYP3A4	Potent inhibitor of CYP3A4
Fluvastatin (synthetic)	40–80 mg daily (23 % with 40 mg)	CYP2C9 (some CYP2C8 and CYP3A4)	Inhibitor of CYP2C9
Rosuvastatin (synthetic)	5–40 mg daily (45 % with 10 mg)	Minimal metabolism (via CYP2C9 and some CYP2C19) and biliary excretion	
Pitavastatin (synthetic)	1–4 mg daily (42 % with 2 mg)	Minimal metabolism (via glucuronidation; marginally via CYP2C9, lesser extent CYP2C8); biliary excretion	Not known

**Typically, doubling of the dose of statin produces an additional 6 % absolute decrease in low-density lipoprotein cholesterol (LDL-C).*
Adapted from Armitage J, Lancet*, 2007.*[126]

in males from this subcontinent.[117] The association of psychosocial risk factors with risk of acute myocardial infarction in 11,119 cases and 13,648 controls from 52 countries (INTERHEART)[118] study reported that MI occurs at 53 years of age in South Asians, five years earlier than in other countries.[119] Moreover, there is an increasing prevalence of CHD in the South Asian population, in migrant Indians as well as native Indians, and this ethnic group is in the middle of a rising epidemic not seen in other ethnic groups.[117,120,121] Traditional risk factors including hypertension, total cholesterol, and LDL-C are highly prevalent in South Asians.[122–124] Furthermore, type 2 diabetes is highly prevalent and central obesity is also on the rise in South Asians.[50,119,125] Since central obesity is an important component of metabolic syndrome, it may be an important factor in the development of CHD in South Asians.[117] Although traditional risk factors are largely responsible for the prevalence of CHD in South Asians, tobacco consumption and diabetes are increasing in this population, which are also contributory factors.[117,125] Additionally, novel factors such as high-sensitivity C-reactive protein (hs-CRP), lipoprotein (Lp)-(a), and small, dense LDL are also prevalent in South Asians.

Environmental changes play a significant part in risk for CHD, particularly in migrating populations, including South Asians moving to Western countries such as the US.[117] A study was conducted in Columbus, Ohio in the US to determine changes in risk factors for CHD in South Asians.[117] Total cholesterol, HDL-C, LDL-C, hs-CRP, Lp(a), TG, homocysteine, and lipoprotein particle numbers were all measured using nuclear magnetic resonance (NMR) spectroscopy. The prevalence of novel risk factors was reported as being considerably higher in South Asians compared with other ethnic groups in the US, which, combined with the high prevalence of traditional factors in this ethnic group, could significantly increase their CHD risk.[117] The prevalence of reduced HDL-C (<40 mg/dl), elevated TG (>130 mg/dl) and small, dense LDL-particles was significantly higher in South Asian women than South Asian men (67.3 versus 49.4 %, 56.4 versus 30.4 %, 53.6 versus 27.8 %; p<0.001 for all risk factors). Furthermore, elevated hs-CRP (>3.0 mg/dl) was more prevalent in women than men (50.6 versus 37.3 %, respectively; p=0.11). A separate study conducted in six ethnic groups in California showed a 16 % rise in all-cause mortality and a 5 % increase in CHD mortality in South Asian women, but a decline in all-cause and CHD mortality in all other ethnic groups.[117]

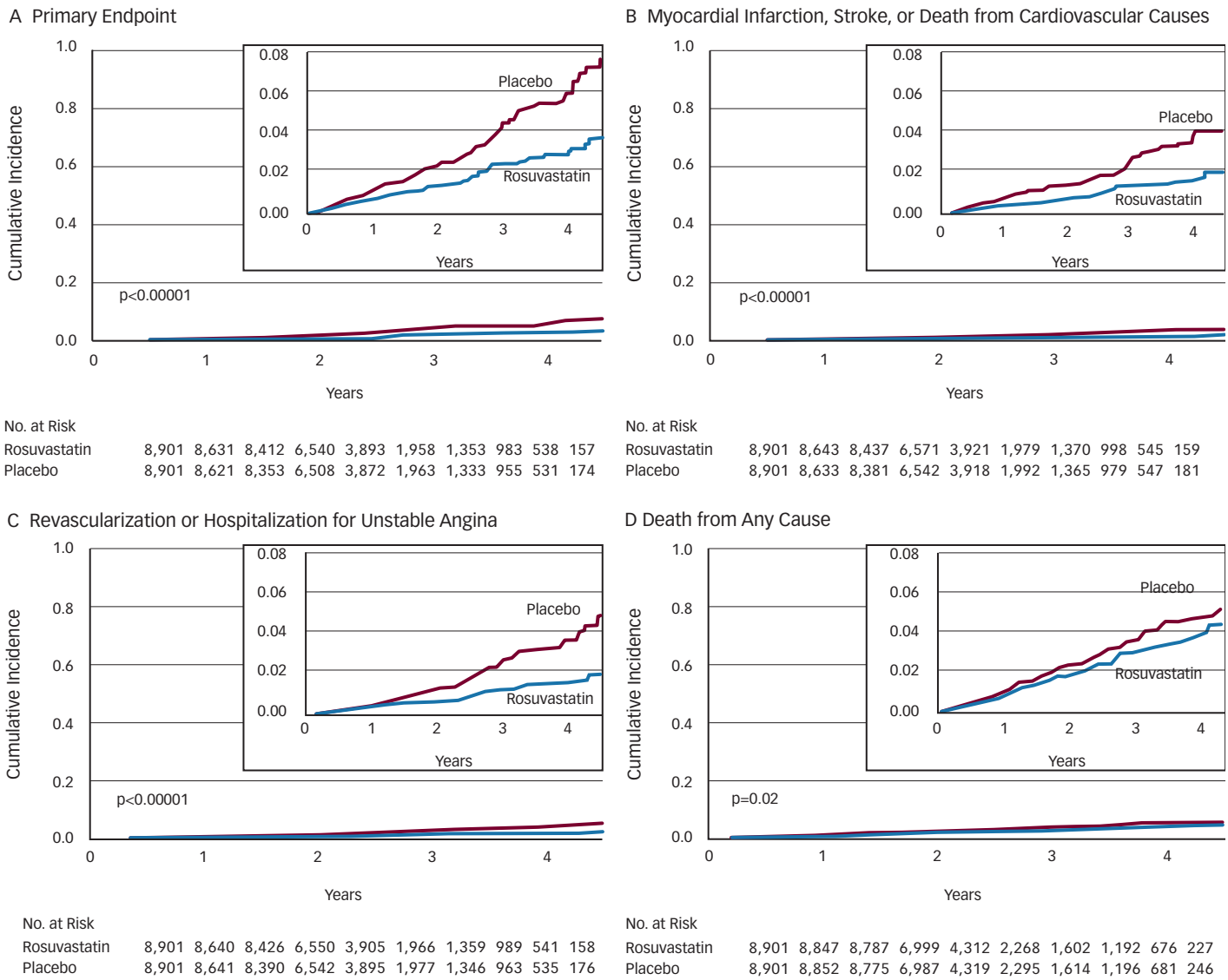
Tolerability Issues with Statins

Different statins have different efficacy and safety profiles (see *Table 1*).[126] The safety and side effects of statins are concerns for patients as well as clinicians. Safety is an important consideration particularly for statin combination therapy,[127] especially in the elderly[128] who are likely to have co-morbidities for which they take multiple medications, causing changes in pharmacokinetics and pharmacodynamics that could alter levels of tolerability, thus affecting adherence to medication.[9] Polypharmacy could also alter elimination of drugs, potentially raising concerns of toxicity.[9] Furthermore, it is important to be aware of the potential side effects of statins, particularly on the liver and muscles.[128] Statin-induced myopathy can occur, although rarely, with the potential to cause rhabdomyolysis.[126] For example, atorvastatin is used to treat dyslipidemia in the elderly, CKD patients and people with type 2 diabetes, and while it is generally well-tolerated, it can have serious adverse effects on the liver and skeletal muscle.[129]

Safety profiles of statins have been studied in the elderly in trials including the Justification for the use of statins in prevention: an interventional trial evaluating rosuvastatin (JUPITER) and the Incremental decrease in endpoints through aggressive lipid lowering (IDEAL) trial.[114,130] The JUPITER study recruited healthy individuals with LDL-C <130 mg/dl and hs-CRP ≥2.0 mg/l who were randomly assigned to rosuvastatin 20 mg daily or placebo.[114] The study cohort was then followed for the occurrence of the combined primary endpoint of MI, stroke, arterial revascularization, hospitalization for unstable angina, or death due to cardiovascular events. Rosuvastatin reduced LDL-C by 50 % and hs-CRP by 37 %. Rosuvastatin significantly reduced the incidence of all major CVD events in all study participants (see *Figure 4*).

The IDEAL study was a prospective, randomized, open-label, blinded endpoint evaluation trial conducted in patients aged ≤80 years with a history of acute MI at 190 ambulatory cardiology care and specialist practises in northern Europe over six years between March 1999 and March 2005.[130] Patients were randomly assigned to high-dose atorvastatin (80 mg/d) or usual-dose (20 mg/d) simvastatin. In this study of patients with a history of MI, intensive LDL-C-lowering did not result in a significant reduction of primary outcome of major coronary events, although it reduced the risk for secondary endpoints and

Figure 4: Cumulative Incidence Of Cardiovascular Events According To Study Group



A: Cumulative incidence of primary endpoint (non-fatal myocardial infarction, non-fatal stroke, arterial revascularization, hospitalization for unstable angina, or confirmed death from cardiovascular causes). Hazard ratio for rosuvastatin compared with placebo was 0.56 (95 % confidence interval [CI] 0.46–0.69; p<0.00001). B: Cumulative incidence of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes, for which hazard ratio in rosuvastatin group was 0.53 (95 % CI 0.40–0.69; p<0.00001). C: Cumulative incidence of arterial revascularization or hospitalization for unstable angina, for which hazard ratio in rosuvastatin group was 0.53 (95 % CI 0.40–0.70; p<0.00001). D: Cumulative incidence of death from any cause, for which hazard ratio in rosuvastatin group was 0.80 (95 % CI 0.67–0.97; p=0.02). In each panel, inset shows the same data on an enlarged y axis and on a condensed x axis.
Adapted from Ridker PM, et al., 2008.[114]

non-fatal acute MI (see *Table 2*). No differences in cardiovascular or all-cause mortality were observed. The outcomes of the study suggest that intensive lowering of LDL-C may be beneficial to MI patients, preventing non-cardiovascular mortality or other serious adverse events.

Statin co-administration with drugs that are also metabolized by CYP can cause adverse drug–drug interactions and an increased risk for side effects.[131] Unlike all the other available statins, pitavastatin is not a substrate for the CYP 3A isoenzymes, as it is primarily metabolized via glucuronidation, thus avoiding the potential for CYP-mediated drug–drug interactions.[72]

Alternative Therapy

There is growing interest in alternative approaches to treating hypercholesterolemia, due to tolerability issues and undesirable effects of conventional treatments such as statins leading to lack of compliance, which are particularly important in the elderly. In particular, the use of red yeast rice[132] and CoQ10[133] have been investigated as alternative ways of reducing cholesterol levels and reducing the degree of muscle pain associated with statin treatment.

Studies on red yeast rice have shown significant effects on LDL-C-lowering with acceptable safety outcomes. However, a recent meta-analysis concluded that although red yeast rice consumption significantly lowered

Table 2: Incidence of and Hazard Ratios for Primary and Secondary Efficacy Outcomes

Outcome Measures	Simvastatin no. (%) (n=4,449)	Atorvastatin no. (%) (n = 4,439)	Hazard Ratio (95% CI)	p-value
Major coronary event (primary outcome)	463 (10.4)	411 (9.3)	0.89 (0.78–1.01)	0.07
CHD death	178 (4.0)	175 (3.9)	0.99 (0.80–1.22)	0.90
Non-fatal myocardial infarction	321 (7.2)	267 (6.0)	0.83 (0.71–0.98)	0.02
Cardiac arrest with resuscitation	7 (0.2)	10 (0.2)		
Any CHD event	1,059 (23.8)	898 (20.2)	0.84 (0.76–0.91)	<0.001
Coronary revascularization	743 (16.7)	579 (13.0)	0.77 (0.69–0.86)	<0.001
Hospitalization for unstable angina	235 (5.3)	196 (4.4)	0.83 (0.69–1.01)	0.06
Fatal or non-fatal stroke	174 (3.9)	151 (3.4)	0.87 (0.70–1.08)	0.20
Major cardiovascular event*	608 (13.7)	533 (12.0)	0.87 (0.78–0.98)	0.02
Hospitalization for non-fatal CHF	123 (2.8)	99 (2.2)	0.81 (0.62–1.05)	0.11
Peripheral arterial disease†	167 (3.8)	127 (2.9)	0.76 (0.61–0.96)	0.02
Any cardiovascular event	1,370 (30.8)	1,176 (26.5)	0.84 (0.78–0.91)	<0.001
All-cause mortality	374 (8.4)	366 (8.2)	0.98 (0.85–1.13)	0.81
Cardiovascular	218 (4.9)	223 (5.0)	1.03 (0.85–1.24)	0.78
Non-cardiovascular	156 (3.5)	143 (3.2)	0.92 (0.73–1.15)	0.47
Malignant disease	112 (2.5)	99 (2.2)	0.89 (0.68–1.16)	0.38
Suicide/violence/accidental death	9 (0.2)	5 (0.1)	…	…
Other	30 (0.7)	32 (0.7)	…	…
Unclassified	5 (0.1)	7 (0.2)	…	…

CHD = coronary heart disease; CHF = congestive heart failure; CI = confidence interval. Ellipses indicate analysis not done because of too few events.
**Major coronary events and stroke.*
†Any newly diagnosed peripheral arterial disease or that which has led to hospitalization.
Adapted from Pedersen et al., 2005.[130]

total cholesterol, LDL-C and TG and increased HDL-C (compared to placebo), many of the trials included in the analysis were of low methodological quality, with poor evidence of randomization and sample size collection, as well as the implication of publication bias.[134] Therefore more robust studies are needed before red yeast rice can be considered as an effective and safe alternative to statins for reducing cholesterol. Statins inhibit HMG-CoA via the same pathway as for the biosynthesis of CoQ10.[133] Therefore, CoQ10 biosynthesis decreases with cholesterol when statin treatment is administered. The decreased CoQ10 production may impair muscle energy metabolism, causing myopathy and muscular symptoms, which are reported in patients on statin treatment.[135,136] Rather than an alternative to statin therapy, CoQ10 could be beneficial if co-administered with statins. A small controlled, double-blinded, randomized pilot study was conducted to test the hypothesis that daily supplementation with CoQ10 could improve muscle symptoms including myopathic pain in patients using statins.[133] Vitamin E supplementation acted as a control in this study. Following 30 days of treatment with CoQ10, pain severity decreased by 40 % ($p<0.001$) and pain interference with daily activities decreased by 38 % ($p<0.02$), compared with no effect observed with vitamin E treatment. The results of this study suggest that statin therapy can be continued in patients who suffer muscle symptoms if CoQ10 is administered as a supplement, although further studies are necessary to draw firm conclusions. Notably, recent studies have identified single nucleotide polymorphisms in co-enzyme Q2 genotypes, as well as genetic polymorphisms in CYP 3A4 inpatients with statin-associated myopathy.[137] Other studies, using vitamin D supplementation while continuing with statin therapy have shown the strategy to be beneficial to help with myopathic symptoms.[138] Other strategies to improve myalgia without true myositis include using low doses of long-acting statins every two to four days or to use less potent statins every other day.[139]

Future of Dyslipidemia Treatment in Special Populations

Although aggressively reducing LDL-C has significantly reduced the number of cardiovascular events, an unacceptable number of CVD events still occur in high-risk patients on treatment.[140] Compliance and tolerability issues are of particular concern in the elderly population. Furthermore, insufficient data exist to direct guidelines for cholesterol-lowering in individuals >75 years of age.[128,141]

Major guidelines recommend statin therapy for the treatment of people with diabetes without CVD, as they are considered to be at equal risk to patients with known CHD. Statins are also recommended for people with other risk factors including older age and microalbuminuria. The ACCORD trial did not establish an additional role for fenofibrate in people with diabetes and lifestyle advice and statins remain the mainstay of lipid therapy in this population.[97] However, even though statins have reduced the incidence of CVD in people with type 2 diabetes, this population still experiences unacceptable levels of morbidity and mortality. Furthermore, this 'residual risk' is much higher in people with co-existing CVD.[97] Newer statins such as pitavastatin have been studied in both type 2 diabetes and metabolic syndrome, with excellent efficacy.[77,142] In addition, the efficacy and safety of pitavastatin have been studied in elderly patients in Phase III studies.[69,143] As a result of its structure and metabolism, pitavastatin could possibly be better tolerated than other statins in these populations who are frequently on polypharmacy drug regiments. Future studies will need to be conducted to see if that is the case.

Summary and Conclusions

One of the main objectives of cardiovascular care is to control LDL-C. Statins are the main-stay for managing dyslipidemia and have proven

high efficacy and satisfactory safety profiles. However, the few known side effects include muscle myalgia, which is particularly common in individuals who often have co-existing conditions and are therefore on multiple medications.

Thus, such side effects are more likely to affect older patients and individuals with conditions such as diabetes, kidney disease, or metabolic syndrome, all of which carry a high risk for CVD. This is also relevant for South Asian populations, who have a high prevalence of traditional and novel CVD risk factors. The latest and seventh statin that has become available, pitavastatin, is not known to cause CYP-mediated drug–drug interactions, which may make it the ideal statin for such individuals who are at a high risk for suffering from severe side effects because of its unique structure metabolism. ■

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