Review Article

Safety of statins

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ABSTRACT

Statins are an established class of drugs with proven efficacy in cardiovascular risk reduction. The concern over statin safety was first raised with the revelation of myopathy and rhabdomyolysis with the use of now withdrawn cerivastatin. Enhanced understanding of the mechanisms behind adverse effects of statins including an insight into the pharmacokinetic properties have minimised fear of statin use among clinicians. Studies reveal that occurrence of myopathy and rhabdomyolysis are rare 1/100000 patient-years. The risk of myopathy/rhabdomyolysis varies between statins due to varying pharmacokinetic profiles. This explains the differing abilities of statins to adverse effects and drug interaction potentials that precipitate adverse effects. Higher dose of rosuvastatin (80 mg/day) was associated with proteinuria and hematuria while lower doses were devoid of such effects. Awareness of drugs interacting with statins and knowledge of certain combinations such as statin and fibrates together with monitoring of altered creatine kinase activity may greatly minimise associated adverse effects. Statins also asymptomatically raise levels of hepatic transaminases but are not correlated with hepatotoxicity. Statins are safe and well tolerated including more recent potent statins such as, rosuvastatin. The benefits of intensive statin use in cardiovascular risk reduction greatly outweigh risks. The present review discusses underlying causes of statin-associated adverse effects including management in high risk groups.

Key words: Myopathy, rhabdomyolysis, safety of statins, statins

Introduction

Statins or 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) inhibitors belong to the class of lipid-lowering agents that revolutionized pharmacotherapeutics of cardiovascular diseases, leading to a remarkable decline in cardiovascular death and disability in patients with or at risk of developing coronary heart disease (CHD).[1] Batteries of clinical trials have investigated the safety and efficacy of statins in reduction of cardiovascular risks. Most trials proclaimed statins safer and tolerable medicine having considerable risk/benefit ratio with the display of only mild and transient adverse effects such as gastrointestinal symptoms, headache, and rashes.[2] The present review discusses mechanisms and safety of statin-induced adverse effects and their management.

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Search Strategy Used

We identified electronic databases, mainly MEDLINE, HighWire, Cochrane, and Google Scholar for articles from 1990 through November 2011 using keywords "3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) inhibitors or Statins," "Safety of Statins," "Adverse Effects of Statins," "Statin-associated Myopathy," "Renal safety of statins," "Mechanism of Statin-Induced Adverse effects," "Management of Statin-induced Adverse effects." In MEDLINE, we used Medical Subject Heading (MeSH) terms: "Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Mesh] AND Safety," "Hydroxymethylglutaryl-CoA Reductase Inhibitors"[Mesh] AND Adverse effects."

Understanding Safety of Statins

Accumulating clinical trial data on safety and efficacy of statins led to framing of guideline by the National

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Cholesterol Education Program and Adult Treatment Panel on use of statins in individuals at high-risk of CHD and other atherosclerotic vascular diseases. High risk patients are prescribed medications for diverse illnesses and often need to take them concurrently leaving enough scope for potential drug-drug interactions, a relevant factor determining the safety profile of statins.[3] Statin possesses differing pharmacological and pharmacokinetic properties and hence differ considerably in safety and has a potential to cause drug-drug interaction. The U.S. Food and Drug Administration (FDA) adverse event report expressed concern over incidence of side-effects, which could be much higher in real clinical situations where patients are not monitored as closely as in clinical trials.[4]

In 2001, the first statin, cerivastatin was withdrawn from market worldwide after confirmed reports of serious myopathy/rhabdomyolysis.[5] The withdrawal sent wave of panic among drug manufacturers and clinicians given the fact that statin by that time had established itself as first-line medicine for reduction of CVD risk. The most important adverse effects associated with statins were asymptomatic increase in hepatic enzymes and musculoskeletal disorders such as myalgia, myopathy, and rhabdomyolysis. Its use caused myalgia in 5% patients, myopathy in 0.1 to 0.2% patients, and rhabdomyolysis in 0.01% patients.[6]

Myopathy

Myopathy or myositis is defined as a diffuse muscle symptom that accompanies elevation of plasma creatine kinase (CK) concentration 10-times higher than the upper limit of normal.[7] It is generally marked by the presence of pain, tenderness, weakness due to severe pain and restriction in mobility. Patients with normal CK levels were also reported to develop myopathic symptoms with statin therapy, indicating that assessment of CK alone cannot adequately predict statin-associated myopathy. Muscle pain in patients taking statins could also occur due to the structural damage of muscle fibers in the absence of elevated CK levels.[8] Though myopathy is a class effect of statins, the potentiality to cause myopathy varies for each statin. In general, these muscular effects have been reported more with the use of synthetic, potent, and more lipophilic statins.[9]

Rhabdomyolysis

Rhabdomyolysis is characterized by marked elevation of CK activity >50-fold, myoglobinemia, myoglobinuria, and myoglobin-induced acute renal failure (oliguria, increased plasma creatinine, potassium, and phosphorus).[10] It is more aggressive and severe form of statin-induced myopathy, resulting in severe skeletal muscle injury, lysis, and excretion of dark brown urine (indicating presence of excess myoglobin release). Rhabdomyolysis alone has been accounted for approximately 10% risk of death due to hyperkalemia-induced arrhythmias or disseminated intravascular coagulation. The risk of rhabdomyolysis was extremely rare and was no more than 5/100000 patient-years.[11] However, considering the prevalence of statin use, even small AE reports would translate into huge health consequences. Patients on lovastatin, simvastatin, and atorvastatin therapy reported higher incidences of rhabdomyolysis. This was due to higher rate of statin metabolism by hepatic microsomal enzymes, cytochrome P3A450 (CYP) isoenzymes. Several commonly prescribed drugs are potent inhibitors of CYP3A4. Concurrent use of statins with these medications increase significantly the risk of rhabdomyolysis as opposed to monotherapy; the risk more often reported in statin-fibrate combination than in statin-niacin combination.[11,12]

Hepatotoxicity

Overall occurrence of statin-induced hepatotoxicity is extremely rare but may be present as asymptomatic elevation of serum transaminases, hepatitis, cholestasis, and acute liver failure (ALF). The mechanism of statin-induced hepatotoxicity is less well-elucidated. Induction of caspase activity, triggering of apoptosis, reduction of coenzyme Q10 (CoQ10), and generation of free radicals have been reported.[13,14] Asymptomatic elevation of hepatic transaminases has been observed in 0.5-2% of patients treated with statins. Statin-induced hepatitis, associated with high levels of transaminases (>3 times the upper limit of normal), hyperbilirubinemia, and clinical symptoms of liver dysfunction was rare and was estimated to be 1/100000 patients-years.[15] Statin-induced ALF was reported to be dose- and time-dependent as reported with other statins, hence making it virtually unpredictable. Potential risk of ALF in vulnerable patients on statin therapy remains unestablished since elevated serum transaminases has no predictive value clinically for ALF.[16] Recently, FDA has recommended revision of labeling instruction for statin and suggested removal of the need for routine periodic monitoring of liver enzymes in patients taking statins. The labels now recommend that liver enzyme tests should be performed before starting statin therapy and as clinically indicated thereafter. FDA reported serious liver injury with statins to be rare and unpredictable in individual patients, and that routine periodic monitoring of liver enzymes did not appear to be effective in detecting or preventing serious liver injury. [http://www.fda.gov/Drugs/DrugSafety].

Nephrotoxicity

Most clinical trials reported renoprotective effects of statins, and only few studies reported moderate proteinuria and hematuria with statins.[10,17,18] The dose of

80 mg/day rosuvastatin caused 12% incidence of proteinuria and occasionally hematuria, which led to subsequent withdrawal of this dose. However, a rosuvastatin dose of 10 mg/day for 12 weeks dosage had no effect on total urinary protein excretion, urinary excretion of albumin or immunoglobulin G. rosuvastatin dose of 20 mg/day showed increased α-1 macroglobulin with no deleterious effect along with enhanced glomerular filtration rate.[17] In a study involving 10,289 patients on rosuvastatin and 1,17,102 on other statins, García-Rodríguez and colleagues reported only 2 out of 14 cases of acute renal failures in patients using rosuvastatin. The relative risk of death associated with use of rosuvastatin compared with other statins was reported as 0.55 (95% CI: 0.44-0.68). The authors did not find any evidence of elevated risk of rosuvastatin-induced adverse effects, including nephrotoxicity when compared to other statins. They also did not find any evidence of increased mortality among patients taking rosuvastatin, even after adjustment of age, sex, and prior statin use.[18] Therefore, as a class, statins were reported to be well-tolerated with no known differences in safety. Though myalgia, myopathy, and rhabdomyolysis occur infrequently but were more common in patients with kidney transplant and with chronic kidney disease (CKD).[19] The effect was dose-related and may be precipitated by agents inhibiting CYP-450 isoenzymes. Hence, caution is warranted while co-administering any statin with drugs that metabolize through CYP3A4, particularly fibrates, cyclosporine, and azole antifungals. Given their demonstrated efficacy and safety record coupled with enhanced understanding, statins must be used in the management of patients with established coronary disease but their use in primary prevention of cardiovascular risk warrants caution in dialysis patients who are at greater risk of toxicity and drug interactions. Elderly patients with CKD are at greater risk of adverse drug reactions and, therefore, the lowest possible dose of statins has been suggested for the treatment of hyperlipidemia. The current guidelines state that statins may be used safely in patients with chronic renal diseases and hemodialysis and suggests dose reduction in severe renal impairment.

Other rare adverse effects

In addition to above statin-associated adverse effects, statin causes several other side-effects, which are comparatively insignificant and rare. They have been summarized in Table 1.[10,11,20-27]

Mechanisms of Statin-Induced Adverse Effects

Statin inhibits mevalonate synthesis by inhibiting enzyme HMG-CoA reductase that catalyzes conversion of HMG CoA to mevalonate [Figure 1]. Mevalonate not only acts as precursor of cholesterol but also serves as a precursor for non-steroid isoprenoids such as CoQ10, heme-A, and farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP). These intermediates of mevalonate pathway impact the benefits as well as risk of statins.[28]

Isoprenoid deficiency

Isoprenoids, FPP, and GGPP are important by-products

Table 1: Other rare adverse effects of statins*

Organ/systems	Statin-induced adverse effects	Reference
Nervous	Hemorrhagic stroke: ↓ LDL-C level → ↑ hemorrhagic stroke; strong data unavailable; risk benefit ratio of statins completely outweighs Peripheral neuropathy: Generally appear after 1-2 months → resolves on discontinuation → low attributable risk Cognitive impairment: Occasionally reported in statin-treated patients → large controlled trials do not confirm Sleep: Sleep disturbances and nightmares	10,11
Cardio-vascular	Vascular reactivity: Statins stimulate vascular CYP2C-derived ROS → inactivation of NO; farnesyl the product of mevalonate cascade deficiency LDL oxidizability: Ubiquinone deficiency → ↑ LDL oxidizability	20
Immune	Induction of apoptosis and release of intracellular antigens (i.e., histones or nucleic acids) → triggers immune response ↑ Auto-antibodies formation → immune response shifts from Th1-mediated (cellular) to Th2-mediated (humoral)	21
Endocrine	Insulin sensitivity: Stimulation of farnesyl and geranylgeranyl transferases both *in vitro* and *in vivo* ↓ Insulin sensitivity and ↑ of plasma insulin concentration after statin therapy Statins impairs insulin signaling and insulin secretion	10
Cancer	Cancer risk: Low coenzyme Q or low serum cholesterol →↑ breast cancer rates	25
Gastrointestinal tract	Rare side-effects: Nausea, dyspepsia, abdominal pain, diarrhea or constipation, gastric ulcer, gallstones	10
Skin	Rare side-effects: Alopecia, rashes, lichenoid eruption, dermographism, chronic urticaria, and toxic epidermal necrolysis	10
Eye	Rarely cause cataract and ocular hemorrhage	26
Reproductive	Rarely cause erectile dysfunction, decrease libido, and gynecomastia	27,28
Blood	↓ Blood clotting → thrombocytopenia and thrombotic thrombocytopenic purpura	29
Respiratory	Rarely cause interstitial lung diseases	30

LDL: Low-density lipoprotein

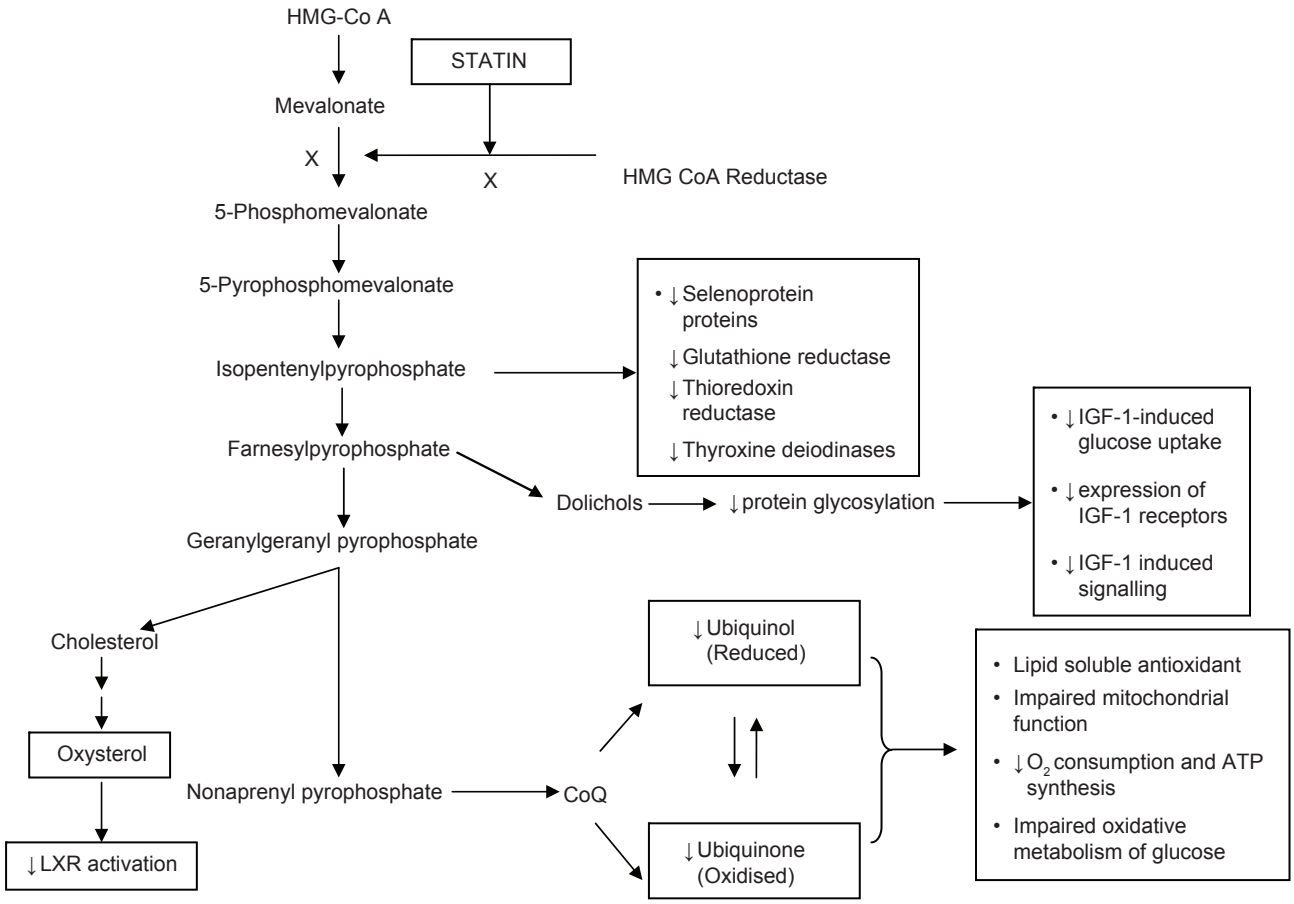

Figure 1: Mevalonate pathway depicting inhibition of downstream intermediate molecules resulting from statin inhibition of mevalonate synthesis. Mevalonate is not only precursor of cholesterol synthesis but also host of other molecules downstream such isopentenylpyrophosphate, farnesylpyrophosphate, geranylgeranyl pyrophosphate, dolichols etc., Statins inhibit HMG-CoA reductase, which catalyzes conversion HMG-CoA to mevalonate. Inhibition of these intermediates leads depletion of various essential molecules cause adverse effects of statins. CoQ: Coenzyme Q; IGF-1: Insulin-like growth factor-1; LXR: Liver X-receptor

of HMG-CoA pathway. These by-products are important component of protein isoprenylation or lipidation, a post-translational modification process where hydrophobic molecules are added to protein and activate them.[9,29] Inhibition of HMG-CoA reductase leads to decreased synthesis of these isoprenoid intermediates affecting protein isoprenylation. Alternatively, statins also promote dysprenylation (protein modification through alternate process). The 2 most important proteins affected are small GTPases and the lamins. Dysprenylation of GTPases ensue a slew of processes, including vacuolation of myofibrils, degeneration and swelling of cellular organelles and ultimately cell death. Reduction of protein isoprenylation also increases cytosolic calcium concentration and activates caspase-3 causing cell death. A role of isoprenoids in statin-induced myopathy was highlighted from the study that reported prevention of apoptosis by isoprenoid administration.[30]

Coenzyme Q

Coenzymes Q (CoQ) consists of 1,4-benzoquinone with a 50-carbon isoprenoid chain derived from FPP. Statin inhibits synthesis of mevalonate, precursor of FPP leading to inhibition of CoQ production. It has also been reported to decrease 20-40% of plasma CoQ10. CoQ10 is a lipid-soluble antioxidant synthesized by mammalian cells and is present as the reduced ubiquinol form and oxidized ubiquinone form (predominant form). It is the only antioxidant capable of regaining its active reduced form upon oxidation. This transition enables CoQ to function as electron carrier in mitochondrial respiratory chain. It acts as cofactor in mitochondrial oxidative phosphorylation and is important for adenosine triphosphate production. Statin-associated myopathy was suggested to result from inhibition of CoQ10 production in mitochondria. CoQ10 deficiency has led to several diseases, including infantile onset multi-systemic diseases, encephalomyopathies with recurrent myoglobinuria, cerebellar ataxia, myopathy, heart failure, Parkinson's disease, and malignancy.[31] It affects children more often than adults. One small clinical trial reported beneficial effect of CoQ10 supplementation in the treatment of statin-induced myopathy.[9]

Sarcolemal cholesterol deficiency

Though still debatable, a deficiency in the level of muscle cell membrane cholesterol has been suggested in alteration of the physical structure of muscle membrane, its integrity, and fluidity. These changes causes an imbalance in the dynamic equilibrium between sarcolemal membrane and plasma cholesterol and hence destabilizes muscle membrane.[32]

Selenoproteins

Selenocysteine synthesis utilizes isopentenylpyrophosphate derived from mevalonate pathway.[10,33] Selenocysteine is required to synthesize selenoproteins such as glutathione peroxidase and thioredoxin reductase (provides antioxidant defense), including thyroxine deiodinases, which catalyzes conversion of thyroxine to triiodothyronine. Statins reduces the availability of isopentenylpyrophosphate, leading to a decrease in production of selenoproteins. Selenium deficiency caused myopathy and cardiomyopathy resembling statin-induced myopathy. Hence, statins-induced deficiency of selenoproteins may impair antioxidant defense and thyroid function.

Dolichols

Dolichols are synthesized from farnesylpyrophosphate and act as carriers for oligosaccharide moiety for protein glycosylation (post-translational modification) required for protein trafficking and function. Statin impairs protein glycosylation by inhibiting dolichol production. One major consequence of statin-induced glycosylation is an impairment of insulin or insulin-like growth factor-1(IGF-1)-induced glucose uptake and proliferation of adipocytes along with reduced expression of glycosylated insulin and IGF-1 receptors and accumulation of unglycosylated receptors in endoplasmic reticulum.[34]

Drug interactions

Statin selectively inhibits HMG-CoA reductase and normally do not show any relevant affinity towards other enzymes or receptors (pharmacodynamic interaction). However, statins show significant pharmacokinetic interaction leading to potential drug-drug interactions.[35] All statins, except pravastatin, are extensively metabolized by liver that involve sets of hepatic microsomal cytochrome P450 isoenzymes. Lovastatin, simvastatin, and atorvastatin are metabolized by CYP3A4; rosuvastatin, and fluvastatin by CYP2C9 isoenzymes; pravastatin through sulfation; and pitavastatin by uridine diphosphate glucuronosyltransferase glucuronidation.[1,9] CYP3A4 isoenzymes are responsible for metabolizing most of the prescribed drugs in the liver. Concomitant use of drug and statin can alter the plasma levels of statins, leading to a risk of myopathy or rhabdomyolysis. However, about 1/3rd of prescriptions for statins are given in combination with drugs with side effects in only 3% of patients.

Both CYP450 inhibitors and inducers play an important role in disposition of statin, in terms of their plasma levels and the risk of statin-induced adverse effects [Table 2].[36] Cytochrome P450 inhibitors are defined as the agents that inhibits the production of the hepatic microsomal enzymes, leading to high plasma levels of statins and greater risk of statin-induced adverse effects like myositis and rhabdomyolysis. Cytochrome P450 inducers are defined as the agents that causes induction of hepatic microsomal enzymes, leading to decrease plasma levels of statins, and hence decreased bioavailability of stain.[1] The common inducers of CYP3A4 isoenzyme were barbiturates, phenytoin, phenobarbital, barbiturates, rifampin, dexamethasone, cyclophosphamide, carbamazepine, omeprazole, and troglitazone, and the common inhibitors were ketoconazole, itraconazole, fluconazole, erythromycin, clarithromycin, tricyclic anti-depressants, nefazodone, venlafaxine, fluvoxamine, fluoxetine, sertraline, cyclosporine A, tacrolimus, mibefradil, diltiazem, verapamil, protease inhibitors, midazolam, corticosteroids, grapefruit juice, tamoxifen, and amiodarone. The common inducers for CYP2C9 were rifampin, phenobarbital, phenytoin, and troglitazone, and the common inhibitors were ketoconazole, fluconazole, and sulfaphenazole. It is well-known that lipophilic nature of a drug influences its absorption and hydrophilic nature helps in excretion. Most statins are lipophilic in nature, except pravastatin and rosuvastatin; explaining their high safety profile over other statins.

Of CYP450 inhibitors, protease inhibitors (amprenavir, indinavir, nelfinavir, ritonavir, saquinavir) are the potent inhibitors of CYP3A4, and its concurrent administration increased plasma statin concentration up to 30-fold; it causes myalgia, rhabdomyolysis, and transaminases elevations.[37] Hence, lovastatin and simvastain are not recommended with PI.

As fluvastatin, pravastatin, rosuvastatin are primarily metabolized by CYP2C9, they are less subject to drug interaction than other statins. In the presence of cyclosporine A, there is 5-23-fold increase in pravastatin bioavailability, leading to reduced biliary clearance of pravastatin and hence increased risk of myopathy. With fluvastatin, cyclosporine A shows milder interaction, which may be due to fluvastatin interaction with CYP2C9.

Intake of grapefruit juice (≥ one liter per day) also increased bioavailability of statins because of the inhibition of intestinal CYP3A4 isoenzyme. The recommended dose for simvastatin and atorvastatin was 10 mg/day, 20 mg/day for lovastatin and 5 mg/day for rosuvastatin due to competition for CYP3A4 when used concurrently with cyclosporine. Similarly, amiodarone dramatically elevated plasma levels of simvastatin levels and, therefore, dose was restricted

Table 2: Safety profiles of statins

Statins	CYP substrate	Cytochrome P3A4		Other interactions
		Inhibitors	Inducers	
Lipophilic statins				
Lovastatin	CYP3A4	Azole antifungals (ketoconazole, itraconazole) Macrolids (erythromycin, clarithromycin, azithromycin) Nefazodone Cyclosporine A Calcium antagonists (mibefradil, diltiazem, verapamil) Protease inhibitors (amprenavir, indinavir etc) Midazolam Mibefradil Grapefruit juice Tamoxifen Amiodarone	Thiazolidenediones anti-diabetic agents	Fibrates Gemfibrozil P-glycoproteins Warfarin
Atorvastatin	CYP3A4	Azole antifungals (ketoconazole, itraconazole) Macrolides (erythromycin, clarithromycin) Nefazodone (anti- depressants) Cyclosporine A Calcium antagonists (mibefradil, diltiazem, verapamil) Protease inhibitors Midazolam Mibefradil Grapefruit juice Tamoxifen Amiodarone	Phenytoin Thiazolidenediones anti-diabetic agents	Fibrates Gemfibrozil P-glycoproteins Digoxin Warfarin
Simvastatin	CYP3A4	Azole antifungals (ketoconazole, itraconazole) Macrolides (erythromycin, clarithromycin) Nefazodone Cyclosporine A Calcium antagonists (mibefradil, diltiazem, verapamil) Protease inhibitors Midazolam Mibefradil Grapefruit juice Tamoxifen Amiodarone	Rifampicin Phenytoin Herbal supplement St. John's wort	Fibrates Gemfibrozil P-glycoproteins Digoxin Warfarin Niacin
Fluvastatin	CYP2C9	Ketoconazole Fluconazole Sulfaphenazole Calcium channel blockers Diclofenac	Rifampin Phenobarbital Phenytoin Troglitazone Thiazolidenediones anti-diabetic agents	Fibrates Niacin Warfarin
Pitavastain	Glucuronidation CYP3A4 and CYP2C9 (minor)	Anti-depressants (nefazodone)	Thiazolidenediones anti-diabetic agents	Fibrates Warfarin
Hydrophilic statins				
Rosuvastatin	CYP2C9 (<10%) and CYP2C 19 (minor)	Ketoconazole Fluconazole Sulfaphenazole	Rifampin Phenobarbital Phenytoin Troglitazone	Fibrates Digoxin Warfarin
Pravastatin	Sulfation	Cyclosporine A		Fibrates Gemfibrozil P-glycoproteins Niacin Warfarin

to 20 mg/day.[9,38] Restrain is warranted in co-prescribing warfarin with statins since fluvastatin and to a lesser extent rosuvastatin are substrates for CYP2C9, which metabolizes warfarin.[38]

Interactions with other agents

Combination of statins and fibrates impairs liver functions, leading to higher levels of statins and hence myopathy. In a study, about 0.12% prevalence of myopathy associated with CK elevations has been found with combination of statins and fibrates.[39] Concurrent gemfibrozil use increased plasma levels of statins by 2-folds.[39] The risk of rhabdomyolysis with gemfibrozil was found to be 10- to 15-fold higher compared to fenofibrate because of differences in fibrate metabolism.[40]

Gemfibrozil-mediated enhancement of myopathic effects was due to competitive inhibition of specific CYP450 and UDP-glucuronosyltransferase (UGT) isoenzymes causing reduced statin clearance. The decrease in statin clearance was due to the competition for glucuronidation, which was required by both statins and fibrates for their metabolism. Statin glucuronidation is an intermediate step in the conversion of active acid forms to lactones and subsequent metabolism by the hepatic CYP450 system.[9]

There was no evidence that niacin and statin combination caused adverse effects greater than risk from individual agents.[1] However, increased risk of myopathy were reported in Chinese population given simvastatin 80 mg/day concurrently with the lipid lowering dose of niacin ≥1 g/day, leading to restriction of simvastatin dose of 40 mg/day in Chinese population on niacin therapy.[41] Statin when given along with ezetimibe increased myopathy.

Transport proteins, P-glycoproteins leads to low bioavailability of atorvastatin, lovastatin, simvastatin, pravastatin, leading to rhabdomyolysis.[1] Co-administration of atorvastatin (80 mg/day) and digoxin (0.25 mg/day) for 20 days increased exposure to digoxin by inhibition of P-glycoproteins.

Management of statin-induced adverse effects

Literature clearly documented increased risk with higher doses and serum concentrations of statins. The reported prevalence of statin-associated adverse effects are less, and among all the available statins, rate of fatal rhabdomyolysis was reported to be less than 1 death/million prescriptions.[42] The National Lipid Association (NLA) Statin Safety Task Force[5] published guidelines regarding the management of statin-associated adverse effects briefly summarized in Table 3.

High Risk/Vulnerable Population to Statin Adverse Effects

Statins are mostly safe, but certain population groups are at an elevated risk of developing statin-associated adverse effects and in whom careful monitoring of statins is recommended.

Alcoholics

There is lack of literature documenting prevalence of statin myopathy among alcoholics; however, excess alcohol intake has been a risk factor for rhabdomyolysis induced by pressure necrosis.[43] In the Heart Protection Study, no upper limit for alcohol consumption was set till the time liver function tests remained within an acceptable range.[44]

Pregnant women

Statins have been contraindicated in pregnancy.[44] Premenopausal women treated with statins were asked to avoid pregnancy or if they so intend, should to stop statin therapy. There have been reports of statins inducing teratogenicity and have caused congenital abnormalities in the babies of women who took statins during early pregnancy. However, further prospective clinical trial collection of data could ascertain further teratogenic potentials of statins.[45,46]

Patients on warfarin

Statins such as simvastatin, fluvastatin, and rosuvastatin

Table 3: Management of statin-associated adverse effects

Muscle effects	NLA does not recommend CK measurement before statin therapy unless individual is at high risk
	Routine CK measurement in asymptomatic patients → not recommended
	Counseling patients on the risk of statin myopathy in symptomatic patients, CK levels should be measured
	CK levels <10 times the ULN: Statin therapy may be continued or dose titration with close monitoring required
	CK level >10 times or 10,000 IU/L the ULN: IV hydration therapy, monitoring of renal function and initiation of treatment for rhabdomyolysis recommended
	CK levels <5 times the ULN → decision to continue statin therapy → based on symptom tolerability; in intolerable case, stopping of statin therapy or reinstitution of therapy with alternate agent or with lower dose once asymptomatic
	In case symptoms rebound → alternate therapy should be considered
Hepatic effects	Hepatic transaminases assessment → before initiation and 12 week after initiation of insulin therapy and Periodical check up
	Measurement of transaminase levels, fractionated bilirubin level and LFT → any overt signs of liver toxicity, such as jaundice, malaise, fatigue, and lethargy
	Transaminase levels between 1 and 3 → In asymptomatic individuals, statin therapy continued with close follow up testing
	Transaminase levels >3 times ULN → Reduction of statin dose or discontinuation of statin therapy while ruling out other causes
	In case of objective evidence of liver injury → Discontinuation of statin therapy and referring patient to gastroenterologist
Renal effects	Regular assessment of serum creatinine and proteinuria → not needed for patients on statin therapy
	Baseline creatinine levels at the initiation of statin therapy → may help to identify patients with underlying kidney disease in high risk patients
	Adjustment in statin doses is recommended → In case of increases in creatinine levels while on statin therapy
	In case of proteinuria detection → consider dose adjustment
	Any abnormal renal indices → assessment of causes other than statin may be looked for
	CKD patients → statin may be administered with close monitoring; dose adjustment in moderate to severe kidney diseases

CK: Creatine kinase, ULN: Upper limit of normal, LFT: Liver function test, CKD: Chronic kidney disease

have been reported to potentiate the anticoagulant effect of warfarin.[47] People requiring warfarin should check their anticoagulation control while initiating, stopping, or modifying statin therapy. However, the change in the required dose of warfarin is small, but occasionally patients may experience clinically relevant changes to their anticoagulant control.

Geriatric patients

Statins have demonstrated benefits in geriatrics in those with CHD and diabetes mellitus.[48] Future studies exploring statin efficacy in primary prevention for patients older than 75-80 years are needed along with better risk assessment tools. From a benefit risk perspective, the benefits of statin therapy in the elderly clearly outweighed the low risk of serious side effects. However, randomized trial data have shown that lowering cholesterol no longer extended life in the elderly, even those at high risk of heart disease. The elderly may be more vulnerable to known adverse effects, and evidence provides cause for concern that new risks may supervene, including cancer, neurodegenerative disease, and heart failure. The impact of statin adverse effects (e.g., muscle and cognitive problems) may be amplified in elderly, and even modest lowering of cognitive and physical function in older elderly may portend increased disability, hospitalization, institutionalization, and mortality.[49] No dose adjustment was recommended despite the fact that geriatrics may be at higher risk of developing myopathy. In randomized trials that included people above 80 year of age, the safety profile and relative benefits of statin treatment have been reported to be similar to those in young adult people. Recent literatures indicate the benefits of statin therapy in the elderly, which outweigh the low risk of serious side effects, still the use of statins in the elderly should be undertaken with circumspection and close scrutiny for any possible adverse effects.

Pediatric patients

There are limited, short-term data demonstrating that statins are apparently safe in children, though long-term follow-up is completely lacking.[50] At an 8 years of age, a child's brain and other organ systems remain in dynamic stages of growth and development, which considerably raise concern that long-term pharmacotherapy initiated at this age may adversely affect the central nervous system, immune function, hormones, energy metabolism, or other systems in unanticipated ways. Recent research suggested that increasing body weight in childhood, even within the range considered normal, was strongly associated with the risk of cardiovascular disease in adulthood.[51] The PLUTO (Pediatric Lipid-redUction Trial of rOsuvastatin) study involving adolescents, age 10 to 17 years along with other studies in nearly 1,000 pediatric patients confirmed that LDL-C lowering with statins was well tolerated in adolescents with familial hypercholesterolemia (FH).[52]

The present body of literatures on statin use in pediatric patients revealed that statins are effective at lowering LDL and TC levels and are fairly well-tolerated for the short-term period in children; therefore, currently an appropriate choice for use in FH as outlined by the clinical report and possibly for other childhood dyslipidemia with elevated TC and LDL levels after lifestyle modifications have been unsuccessful. However, appropriate monitoring of drug adverse effects and growth and development should occur in all patients.[53]

Cardiac patients

Some reports noted harmful effects of statins in patient with cardiac failure since it was observed that low cholesterol are associated with poor outcome in such patients.[54] One large study showed high levels of N-terminal pro-B type natiuretic peptide (N-BNP), which was predictive of cardiac failure, received similar cardiovascular benefits with simvastatin compared with patients without cardiovascular hazard.[55]

Kidney function

Although statins are considered safe in moderate renal impairment, but patients having glomerular filtration rate in the range of 30-60 mL/min were at a higher cardiovascular risk. Data suggests statins beneficial in these subgroups, but they may be at a higher risk of myopathy. One trial showed no cardiovascular benefits with atorvastatin 20 mg/day in patients with diabetes on maintenance hemodialysis; therefore, role of statins for the prevention of cardiovascular disease in patients with chronic kidney disease is less well-understood).[56]

A meta-analysis of 36 studies that included 40,600 participants assessed the effects of rosuvastatin on the renal safety. The study suggested that intensive LDL-C-lowering treatment with rosuvastatin did not affect the risk of developing renal insufficiency or renal failure in patients who do not have advanced, pre-existing renal disease.[57] The study supported that rosuvastatin may be safely used in renal-compromised patients.

Increasing Safety of Statins

Statins may be classified into 3 categories based on their increasing potency and efficacy in lowering plasma low-density lipoprotein cholesterol (LDL-C) concentration. The first generation statins included lovastatin, pravastatin, and fluvastatin; simvastatin and atorvastatin among second

generation; and rosuvastatin and pitavastatin among third generation statins.

First generation statins

The first generation statins (FGS) were introduced during the late 1980s and 1990s, and this class of statins had the lowest potency. Among FGS, pravastatin was the most studied statin, and several clinical trials showed reduction in LDL-C levels, cardiac mortality, and coronary events.[58] In secondary prevention and symptomatic coronary disease patients too, pravastatin was proved to be effective. Though the adequate evidence is lacking, lovastatin and fluvastatin also demonstrated benefited cardiovascular risk reduction. In the FGS, pravastatin and fluvastatin commanded much attention because of their low drug interaction as they are not metabolized by CYP450 isoenzyme systems. Hence, in spite of their low potency, they are used as an alternative in patients who are intolerant to potent statins.

Second generation statins

The second generation of statins (SGS) was marked by introduction of atorvastatin and simvastatin. Even today, they are considered as the best selling statins. These statins had superior efficacy in lowering plasma LDL-C levels than FGS. The daily doses of only 10 mg atorvastatin and 20 mg simvastatin caused greater than 30% lowering of LDL compared with 20-40 mg daily doses of FGS. Battery of trials demonstrated their use in both primary and secondary trials. Trials to study intensive versus moderate statin therapy for maximizing LDL-C lowering and to achieve better cardiovascular outcomes would be possible only with the availability of more potent and superior SGS. Intensive statin therapy was mostly directed at secondary prevention patients who mostly were benefited from aggressive lipid-lowering agents. The pharmacological demonstration of atorvastatin and simvastatin drug-drug interaction is now well-established and had raised many eyebrows in the use of SGS in high-risk patients. However, various clinical trials demonstrated adequate safety and efficacy of aggressive lipid-lowering in high-risk patients with SGS.[59-62] Wider information on statin drug interactions and monitoring of the statin adverse effects would further help in minimizing statin-induced myopathy.

Third generation statins (rosuvastatin)

Third generation statins (TGS) included rosuvastatin and pitavastatin, which had high potency and efficacy and thus termed as super statins.[58] Rosuvastatin owes remarkable potency and efficacy due to its fluorinated phenyl group and hydrophilic methane sulphonamide group in addition to the common dihydroxyheptenoic acid side chain. Its unique chemical structure enables multiple and strong binding with HMG-CoA reductase enzyme. It has low drug interaction potential due to its hydrophilic nature, which avoids biotransformation for conversion into water-soluble intermediates for elimination.[62] Pitavastatin also have several clinical advantages over FGS and SGSs. It's lowering potentiality of serum LDL-C was greater than pravastatin but was similar to atorvastatin. It is primarily metabolized through glucuronidation, and only minor fractions are metabolized by CYP2C9 and CYP3A4. Therefore, pitavastatin is hardly metabolized by microsomal cytochrome P450 system compared to other statins and hence has an advantage of not having unexpected interactions with other drugs. These TGSs are used as an alternative to other statins in high-risk patients who more often develop statin intolerance.

Conclusion

Almost all the statin trials reported statins to be safe and tolerable. However, in the August 2001, withdrawal of cerivastatin caused widespread ripples among clinicians because of their wide usage in reduction of cardiovascular morbidity and mortality. The revelation that statins may cause fatal rhabdomyolysis raised questions on the safety of statin. Later, several clinical trials dispelled this notion, and the current guidelines suggested dose reduction and halting of statin therapy only in extreme conditions. Subsequent to the rise of safety issues, new potent statins such as rosuvastatin has been scrutinized regarding high dose (80 mg/day) that caused proteinuria and hematuria. However, these effects were transient and reversible, requiring just the reduction of the dosage. The understanding of relatively common statin-associated adverse effects will enable clinicians in making decision in choosing out appropriate statin for their patients giving due consideration to the fact that benefits of statins greatly outweigh its risks.

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