GENES POLYMORPHISM THAT MODIFY CARDIOVASCULAR DRUGS ACTION

COMPETITIVE INHIBITORS OF HMG-COA REDUCTASE (REDUCTASE INHIBITORS: “STATINS”)

These compounds are structural analogs of HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A). Lovastatin, atorvastatin, fluvastatin, pravastatin, simvastatin, rosuvastatin, and pitavastatin belong to this class. They are most effective in reducing LDL. Other effects include decreased oxidative stress and vascular inflammation with increased stability of atherosclerotic lesions. It has become standard practice to initiate reductase inhibitor therapy immediately after acute coronary syndromes, regardless of lipid levels.

Lovastatin and simvastatin are inactive lactone prodrugs that are hydrolyzed in the gastrointestinal tract to the active β-hydroxyl derivatives, whereas pravastatin has an open, active lactone ring. Atorvastatin, fluvastatin, and rosuvastatin are fluorine-containing congeners that are active as given. Absorption of the ingested doses of the reductase inhibitors varies from 40% to 75% with the exception of fluvastatin, which is almost completely absorbed. All have high first-pass extraction by the liver. Most of the absorbed dose is excreted in the bile; 5–20% is excreted in the urine. Plasma halflives of these drugs range from 1 to 3 hours except for atorvastatin (14 hours), pitavastatin (12 hours), and rosuvastatin (19 hours).

HMG-CoA reductase mediates the first committed step in sterol biosynthesis. The active forms of the reductase inhibitors are structural analogs of the HMG-CoA intermediate that is formed by HMG-CoA reductase in the synthesis of mevalonate. However, the reductase inhibitors clearly induce an increase in high-affinity LDL receptors. This effect increases both the fractional catabolic rate of LDL and the liver’s extraction of LDL precursors (VLDL remnants) from the blood, thus reducing LDL. Because of marked first-pass hepatic extraction, the major effect is on the liver. Preferential activity in liver of some congeners appears to be attributable to tissue-specific differences in uptake. Modest decreases in plasma triglycerides and small increases in HDL also occur. Clinical trials involving many of the statins have demonstrated significant reduction of new coronary events and atherothrombotic stroke. Mechanisms other than reduction of lipoprotein levels appear to be involved. The availability of isoprenyl groups from the HMG-CoA pathway for prenylation of proteins is reduced by statins, resulting in reduced prenylation of Rho and Rab proteins. Prenylated Rho activates Rho kinase, which mediates a number of mechanisms in vascular biology. The observation that reduction in new coronary events occurs more rapidly than changes in morphology of arterial plaques suggests that these

pleiotropic effects may be important. Likewise, decreased prenylation of Rab reduces the accumulation of Aβ protein in neurons, possibly mitigating the manifestations of Alzheimer's disease.

Reductase inhibitors are useful alone or with resins or niacin in reducing levels of LDL. Women with hyperlipidemia who are pregnant, lactating, or likely to become pregnant should not be given these agents. Use in children is restricted to selected patients with familial hypercholesterolemias. Because cholesterol synthesis occurs predominantly at night, reductase inhibitors—except atorvastatin, rosuvastatin, and pitavastatin—should be given in the evening. Absorption generally (with the exception of pravastatin and pitavastatin) is enhanced by food. Daily doses of lovastatin, pravastatin, simvastatin, and atorvastatin vary from 10 to 80 mg.

Adverse effects. Elevations of serum aminotransferase activity (up to three times normal) occur in some patients. This is often intermittent and usually not associated with other evidence of hepatic toxicity. Therapy may be continued in such patients in the absence of symptoms if aminotransferase levels are monitored and stable. In some patients, who may have underlying liver disease or a history of alcohol abuse, levels may exceed three times normal. This finding portends more severe hepatic toxicity. These patients may present with malaise, anorexia, and precipitous decreases in LDL. Medication should be discontinued immediately in these patients and in asymptomatic patients whose aminotransferase activity is persistently elevated to more than three times the upper limit of normal. These agents should be used with caution and in reduced dosage in patients with hepatic parenchymal disease, north Asians, and the elderly. Severe hepatic disease may preclude their use. In general, aminotransferase activity should be measured at baseline, at 1–2 months, and then every 6–12 months (if stable).

Monitoring of liver enzymes should be more frequent if the patient is taking other drugs that have potential interactions with the statin. Excess intake of alcohol tends to aggravate hepatotoxic effects of statins. Fasting plasma glucose levels tend to increase 5–7 mg/dL with statin treatment. Long-term studies have shown a small but significant increase in the incidence of type 2 diabetes in statin-treated patients, most of whom had findings of prediabetes before treatment.

Minor increases in creatine kinase (CK) activity in plasma are observed in some patients receiving reductase inhibitors, frequently associated with heavy physical activity. Rarely, patients may have marked elevations in CK activity, often accompanied by generalized discomfort or weakness in skeletal muscles. If the drug is not discontinued, myoglobinuria can occur, leading to renal injury. Myopathy may occur with monotherapy, but there is an increased incidence in

patients also receiving certain other drugs. Genetic variation in an anion transporter (OATP1B1) is associated with severe myopathy and rhabdomyolysis induced by statins. Variants in the gene (*SLCO1B1*) coding for this protein can now be assessed.

The OATP1B1 transporter (encoded by the *SLCO1B1* gene) is located on the sinusoidal membrane (facing the blood) of hepatocytes and is responsible for the hepatic uptake of mainly weakly acidic drugs and endogenous compounds, eg, statins, methotrexate, and bilirubin. Over 40 nonsynonymous variants (nsSNPs) have been identified in this transporter, some of which result in decreased transport function. A common reduced function polymorphism, rs4149056, has been shown to reduce transport of OATP1B1 substrates in vitro as well as to alter pharmacokinetic and clinical outcomes in vivo. The variant results in an amino acid change, Val174Ala, and is associated with reduced membrane expression, likely as a result of impaired trafficking capability. Allele ∗5 is relatively rare (rs4149056 alone; ∼1%), but various other reduced function alleles (∗15 and ∗17; haplotypes containing rs4149056) are common in most European and Asian populations (between 5% and 15%). For patients with a normal genotype and OATP1B1 activity, the usual standard dose of simvastatin is prescribed; in individuals with OATP1B1 loss of function (one or both non-functioning alleles), CPIC (Clinical Pharmacogenetics Implementation Consortium) recommends reducing the dose of simvastatin or using another statin.

The catabolism of lovastatin, simvastatin, and atorvastatin proceeds chiefly through CYP3A4, whereas that of fluvastatin and rosuvastatin, and to a lesser extent pitavastatin, is mediated by CYP2C9. Pravastatin is catabolized through other pathways, including sulfation. The 3A4-dependent reductase inhibitors tend to accumulate in plasma in the presence of drugs that inhibit or compete for the 3A4 cytochrome. These include the macrolide antibiotics, cyclosporine, ketoconazole and its congeners, some HIV protease inhibitors, tacrolimus, nefazodone, fibrates, paroxetine, venlafaxine, and others (see Chapters 4 and 66). Concomitant use of reductase inhibitors with amiodarone or verapamil also causes an increased risk of myopathy.

Conversely, drugs such as phenytoin, griseofulvin, barbiturates, rifampin, and thiazolidinediones increase expression of CYP3A4 and can reduce the plasma concentrations of the 3A4-dependent reductase inhibitors. Inhibitors of CYP2C9 such as ketoconazole and its congeners, metronidazole, sulfinpyrazone, amiodarone, and cimetidine may increase plasma levels of fluvastatin and rosuvastatin. Pravastatin and rosuvastatin appear to be the statins of choice for use with verapamil, the ketoconazole group of antifungal agents, macrolides, and cyclosporine. Doses should be kept low and the patient monitored frequently.

Plasma levels of lovastatin, simvastatin, and atorvastatin may be elevated in patients ingesting more than 1 liter of grapefruit juice daily. All statins undergo glycosylation.

Creatine kinase activity should be measured in patients receiving potentially interacting drug combinations. In all patients, CK should be measured at baseline. If muscle pain, tenderness, or weakness appears, CK should be measured immediately and the drug discontinued if activity is elevated significantly over baseline. The myopathy usually reverses promptly upon cessation of therapy. If the association is unclear, the patient can be rechallenged under close surveillance. Myopathy in the absence of elevated CK can occur. Rarely, hypersensitivity syndromes have been reported that include a lupus-like disorder, dermatomyositis, peripheral neuropathy, and autoimmune myopathy. The latter presents as severe pain and weakness in proximal muscles that does not remit when the statin is discontinued. It is HMG-CoA reductase antibody positive and requires immunosuppressive treatment.

Reductase inhibitors may be temporarily discontinued in the event of serious illness, trauma, or major surgery to minimize the potential for liver and muscle toxicity. Use of red yeast rice, a fermentation product that contains statin activity, is not recommended because the statin content is highly variable and some preparations contain a nephrotoxin, citrinin. The long-term safety of these preparations, which often contain a large number of poorly studied organic compounds, has not been established.

The antiarrhythmic drug **propafenone** (class IA) is metabolized in the liver by CYP2D6. In *slow metabolizers*, the metabolism of propafenone slows down and this leads to an increase in the concentration of the drug in the blood and an increase in the likelihood of side effects (arrhythmias). **Procainamide** is a class IA antiarrhythmic drug metabolized by N-acetyltransferase (NAT). With the genotype of *slow metabolizers* ("*slow acetylators*"), the concentration of novocainamide in the blood increases, which can increase the severity of side effects. The antiarrhythmic agent amiodarone, which is metabolized in the liver with the participation of CYP2D8, can accumulate in the blood and cause and increase unwanted effects in "*slow metabolizers*".

Beta-blockers (carvedilol, metoprolol, nebivolol, propranolol) are metabolized in the liver with the participation of the CYP2D6 enzyme; the presence of the genotype of "*slow metabolizers*" will contribute to an increase in their concentration in the blood and, accordingly, an increase in the risk of unwanted effects.

The hypotensive agent **hydralazine** undergoes acetylation in the liver with the participation of the N-acetyltransferase enzyme; "*slow acetylators*" may experience changes in the concentration of the original substance (growth) and its metabolite in the patient's body, which in turn increases the frequency of unwanted effects (for example, pseudosystemic lupus erythematosus, etc.). Anti-gout agent allopurinol in *HLA-B *58:01* allele positive individuals may cause high risk of adverse reaction (severe skin reactions).