A CASE STUDY OF A WOMAN WITH STATIN-RELATED MYOSITIS

Dr Wang Theng Tan, Dr Tan Ngiap Chuan

Mdm G is a 63-year-old Chinese lady with a history of hyperlipidemia, type II diabetes mellitus, hypertension and osteoarthritis of the knees. She was referred from a regional hospital to be followed up in a primary care center in Singapore. She was initially treated in the hospital with Simvastatin (@Zocor) 20mg on but was subsequently reduced to 5mg eon in primary care as her latest LDL was 1.17mmol/L. Her other medications included Enalapril 7.5mg om, Nifedipine (@Adalat) LA 30mg om, Metformin Retard 850mg bd, and subcutaneous insulin (@Mixtard 30/70) 18U bd. Her Hba1c was 8.3%, urine protein trace on Lapstix; creatinine and liver function were normal. Diabetic eye and feet screening did not reveal any evidence of microvascular complications. However, she had hypotonic bladder, which predisposed her to increased residual urine and recurrent urinary tract infection. The urologist treated her with Distigmine (@Ubretid) 5mg eod.

Mdm G was seen at the hospital emergency department for low back pain of 2 days' duration associated with a positive left punch. No lower limb symptom was present. She had pyuria with urine microscopy showing RBC 15, WBC 720 but EC 0. She was admitted and treated with intravenous ceftriaxone. Both her urine and blood culture grew E. coli sensitive to ceftriaxone and ciprofloxacin. She developed fever, which persisted despite IV ceftriaxone. Ultrasound kidneys did not show pyonephritis, pyonephrosis or hydronephrosis. IV ciprofloxacin was added in view of urine culture result. However, she had persistent myalgia. Creatine kinase (CK) level was elevated at 15345 U/L (Reference lab CK ULN was 164 U/L). Chest x-ray and ECG were normal. Myoglobulinuria was not noted. She was diagnosed with myositis secondary to statin (hydroxymethyl glutaryl coenzyme A reductase inhibitors). She was taken off the statin and was hydrated intravenously. Renal function tests remained normal and CK levels declined. She was discharged well and was followed up subsequently at the hospital specialist clinic.

Discussion

Mdm G developed myositis despite tailoring down to very low dose of statin. She had multiple risk factors for coronary vascular diseases, which necessitated the continuation of statin. Could we have prevented this potentially life-threatening incident through routine laboratory monitoring? This review paper focuses on the use, safety, clinical and laboratory monitoring of the potential ill-effects of statins.

Why is statin indicated for patients with high risk of macrovascular complications?

Statins are the most effective medications for lowering low-density lipoprotein cholesterol (LDL-C), which is implicated in vascular disease. Large clinical trials have demonstrated that statins reduce risk for major coronary events (myocardial infarct and unstable angina) by at least one third. Total mortality, revascularisation procedures, stroke and peripheral vascular disease are also reduced in patients treated with statins in these trials[1-8].

Based on the findings of the Heart Protection Study[4], if 1000,000 high-risk patients were to put on statin, approximately 5000 deaths would be prevented annually. This would translate into approximately 70 to 100 fewer myocardial infarcts, strokes or revascularisation operations for every 1000 patients with CHD, other vascular disease or diabetes treated with statins for 5 years (7% to 10% absolute risk reduction). In fact, statins have been shown to benefit people in all subgroups - patients with or without established CHD, men and women, middle-aged and older persons, persons with and without risk factors including diabetes mellitus, and people with mildly elevated as well as higher LDL-C levels[1-8].

In accordance to the NCEP ATP III guidelines in 2001[9], a greatly expanding number of patients would require statin therapy, and many patients would require relatively high doses of statins to achieve LDL-C goals of therapy. New recommendations from the NCEP have proposed an LDL-C goal of < 1.81 mmol/L for very high risk patients[10]. Changing concepts of benefits from statin therapy towards more aggressive treatment goals for lowering LDL-C have led to the increasingly widespread use of the medication. Hence, increased attention has to be given to every aspect of statin therapy, including its safety. As such, Mdm G's case highlighted the side effects of one of the most commonly used medication in our practice.

Which are the potential muscle-related complications of statins?

Statin therapy has been well tolerated in millions of patients over 15 years of clinical use. One notable side effect of statin therapy is myopathy. In the worst cases, severe rhabdomyolysis, myoglobinuria, acute renal failure and even death can occur. While rare, myopathy and rhabdomyolysis have been reported for all statins. In fact, cerivastatin was withdrawn from the market in 2001 by its manufacturer due to the relatively high reporting rate for rhabdomyolysis (10 to 50 times higher than

TAN WANG THENG, Medical Officer, SingHealth Polyclinics - Pasir Ris

TAN NGIAP CHUAN, Director, SingHealth Polyclinics - Pasir Ris

other statin monotherapy) and fatalities[12]. This has sparked great interest and concern in physicians and patients alike regarding the safety of the statins. There were no clinically significant differences in the reported rate of fatal complications among atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin in the FDA Adverse Event Reporting System[12].

The terminology used for statin-related muscle complications has been inconsistent among various studies and reports, but is important in helping us making clinical decisions in our practice.

According to National Institute of Neurological Disorders and Stroke (NINDS) Myopathy Page, myopathy is a general term referring to any disease of muscles; it can be acquired or inherited, and can occur at birth or later in life. Thompson et al. in their review article in *JAMA*[13] have attempted to separate statin-associated muscle problems into 6 different syndromes: clinically important myositis and rhabdomyolysis, mild CK elevations, myalgia, muscle cramps, muscle weakness, and persistent myalgia or CK elevations after statin withdrawal.

What are the differences between myositis and rhabdomyolysis?

Clinically important myositis in most studies is defined as muscle pain with elevated CK levels more than 10 times the ULN[14]. The incidence of clinical important myositis is very low at approximately 0.1% in clinical trials on statin[11].

In this case, Mdm G did have clinically significant CK elevations or myositis. Although CK elevation more than 10 times ULN may be associated with myoglobinuria, but greater degrees of muscle damage and CK elevations (often >100 times ULN) are usually required to cause pigment-induced renal failure, and some patients (like Mdm G) experience great increases in CK levels without renal complications[15]. Hence, the occurrence of rhabdomyolysis may not be related to the degree of muscle injury alone, but also the patient's hydration status and possibly factors like concomitant medications and genetic predisposition[13]. More recently, the FDA has defined rhabdomyolysis as an appropriate diagnosis only when organ damage (typically renal insufficiency) occurs in association with elevated CK levels. Hence, the diagnosis of rhabdomyolysis should be made if there is muscle symptom, with clinically significant CK elevation (typically substantially greater than 10 times ULN), and creatinine elevation (usually with brown urine and urinary myoglobin)[11].

The risk of fatal rhabdomyolysis is estimated at 0.15 deaths per 1 million prescriptions[12]. Although the adverse effects of statins outside of clinical trials have not been fully reported, the incidence of side effects may be higher in clinical situations since the patients are not monitored as closely as they are in trials.

The association between statins and rhabdomyolysis is dose dependent[16], and the risk increases when statins are used in combination with agents that are also myotoxic or those that increase the serum concentration of statin (Table 1).

Table 1. Drug interactions with statins

Fibrates (especially gemfibrozil)
Nicotinic acid (rarely)
Cyclosporin
Azole anti-fungals
Macrolide antibiotics
HIV protease inhibitors
Verapamil
Amiodarone
Nefazodone (anti-depressant)
Large amounts of grape juice (usually more than 1 quart per day)
Alcohol abuse

Patients with complex medical problems, on multiple medications, with concurrent risks for myopathy (eg. alcohol abuse, excessive exercise, acute viral infections, major trauma or surgery, hypothyroidism), or those with a smaller volume of distribution (eg. elderly and women), are at increased risk of developing rhabdomyolysis with statin therapy[11,13,14,16-19].

Mild CK elevations (do not exceed 10 times ULN) occur more frequently. These patients may be asymptomatic, and may be detected on routine testing or evaluation of other conditions. The incidence of mild CK elevation is not known as it is rarely reported in clinical studies. It is also difficult and frustrating for the physician as such CK elevations are non-specific and can frequently occur after IM injections (eg. IM diclofenac for pain), exercise (especially when statin can magnify the increase in CK levels), and myocardial infarct. The CKMB level is usually not elevated in statin myopathy[13].

Can statin cause myalgia?

Myalgia is defined as muscle pain that affects patients' quality of life and compliance with medications. It is generally not associated with increased CK levels. This is a common compliant by patients, but is again non-specific. Myalgia was reported to have contributed to 19% to 25% of adverse events associated with statin use in a recent review of a database[20,21].

However, in placebo-controlled trials, the incidence of myalgia (about 5%) is similar between statin and placebo, suggesting that it may not be statin-induced[11,22,26]. Nevertheless, the temporal association between statin therapy and complaint of myalgia was strong enough to implicate the drug as a cause in some patients. Some patients respond to statin withdrawal, further implicating these medications.

Reports of persistent myalgia with CK elevation after withdrawal of statin is also rare[25]. These patients may have other underlying problems, such as polymyalgia rheumatica, temporal arteritis and hypothyroidism, which have been unmasked by the statin. Hence, they may benefit from further investigations.

Is muscle cramp or weakness a statin-related complication?

Muscle cramps have been reported in 1% of patients taking lovastatin (40 mg) as compared to 0.5% of patients on placebo[23]. An interesting study by Philips et al suggests that statin-induced myotoxicity can occur without CK elevations[24]. In this study, 4 out of 20 patients on statin, developed muscle pain and quantitatively measured muscle weakness that resolved after they were taken off the statin and placed on placebo. Muscle biopsies on 3 of these patients showed changes of myopathy that resolved after statin withdrawal as well. However, these results are clearly preliminary; and this is a small study and all appropriate controls were not used.

Do statins cause liver complications?

Hepatotoxicity is another major concern. Two hepatic abnormalities are noted to be associated with the use of statins – asymptomatic transaminase elevations, and rare hepatotoxic reactions manifested primarily by cholestatic or mixed injury with very rare cases of acute liver failure (ALF)[28].

Asymptomatic Alanine transaminase (ALT) and Aspartame transaminase (AST) elevations greater than 3 times ULN are observed in about 0.5 to 2% of patients receiving statins[6,22]. The transaminase elevation in the pre-marketing trials of lovastatin was characterized by minor elevations in ALT that were almost uniformly greater than AST and not associated with elevations in alkaline phosphatase or bilirubin. This effect is dose dependent, and it does not appear to be associated with hepatic injury[6,28]. The biochemical changes often resolve with a reduction in dose, and elevations often do not recur with re-challenge or usage of another statin.

Furthermore, Angulo reported that statins did not worsen outcomes in patients with chronic transaminase elevations caused by hepatitis B or C, even though concurrent cholestasis and active liver disease are listed as contraindications to statin use[29]. In fact, treatment of hyperlipidemia in these patients may even improve transaminase elevations in fatty liver.

Amongst the 4,444 patients involved in the Scandinavian Simvastatin Survival Study[1], 1.8% of the patients in the simvastatin group and 1.4% in the placebo group had elevated ALT levels more than 3 times ULN and continued the study. None of these patients developed serious liver disease, suggesting that minor asymptomatic ALT elevations were not predictive of significant liver disease. Similar findings were obtained from the AFCAPS/TexCAPS study using lovastatin[6].

Many of the patients who require statin therapy may have non-alcoholic steatohepatitis secondary to type II DM, dyslipidemia, or obesity as well. This could also account for mild fluctuating elevations in ALT in some patients. Of course, alcohol can also commonly produce this pattern, as can any of the common viral hepatitides. The net result is that, in the majority of patients on statins with asymptomatic elevated transaminases, there is often another perfectly adequate cause for the finding. This accounts for the fact that in virtually all of the clinical trials, transaminitis is as common in the placebo group as in the statin group.

Statins are highly liver specific and therefore inhibits cholesterol synthesis in the liver to a higher degree than in any other tissue. Minor ALT and AST elevations are observed with the other classes of lipid-lowering agents as well. The ubiquity of these elevations suggests that the increase may be due to changes in lipid metabolism induced by the lipid-lowering drugs and not by the drugs themselves. The fact that histologic injury does not seem to occur with elevations in ALT suggests that hepatic adaptation or tolerance occurs rapidly, thus preventing significant injury.

What are the incidences of liver abnormalities associated with statins?

Reports of hepatotoxic reactions are rare. Very rare cases of ALF have been reported with all the cholesterol-lowering drugs. According to the Merck Worldwide Adverse Events System (WAES) and FDA database, the rate with lovastatin is approximately 1/1.14 million patient-treatment years, which is 9% of the background rate of all causes of ALF and approximately equal to the background rate of idiopathic ALF[28]. There is, however, no dispute that the risk of ALF caused by statins, if it exists, is very low. It is an idiosyncratic reaction, and therefore, is by definition not predictable. There is currently no evidence that minor asymptomatic transaminitis precede ALF. Moreover, the clinical course of ALF is so short (ie. within days) that infrequent monitoring (intervals of months) would be of no value.

There were 232 reports of "acute hepatitis" in the WEAS database for lovastatin. The only evidence of hepatitis was elevated ALT in many cases, and almost half of the 60 liver biopsies done showed evidence of other forms of liver disease (eg. autoimmune hepatitis). Assuming all these 232 cases were drug related, the incidence of hepatitis would be about 1/100,000 patient-years of exposure, which is considerably less than that associated with other commonly used medications such as NSAIDS (between 2.2 to 50/100,000 patient-years)[28]. The estimated rate of cholestatic reactions to statin is 1 per 153,000 patient-years. To detect these cholestatic reactions, alkaline phosphatase and bilirubin should be measured, but they are usually not done in clinical practice. Moreover, patients with cholestatic reactions are symptomatic (pruritus and jaundice), which bring them to medical attention before serious liver injury occurs.

Do we need to screen for statin related liver abnormalities? The accuracy of a screening test depends not only on the sensitivity and specificity of the test, but also on the prevalence of the condition in the target population. If the target condition is rare, even tests with excellent sensitivity and specificity will produce a large number false-positive result. For instance, if the prevalence of drug-induced liver disease was 1/5000 and even assuming screening for an elevated ALT was 100% sensitive and 99% specific, 98% of all positive tests would be false positive according to Tolman's calculations[28].

If the risk of hepatic injury based on an asymptomatic ALT elevation is much lower than the likelihood of benefit from reduction in the risk of vascular disease, more patients will be

harmed than helped if they were removed from statin therapy. False positives also create financial costs for the patients, their employers and the healthcare system. Due to the high rate of false-positive results combined with the low likelihood of producing a favourable health outcome, many hepatobiliary experts are suggesting that periodic liver monitoring is overly expensive and not cost-effective[27,28,30-32]. There is currently no clear evidence for routine ongoing monitoring of CK for myopathy as well.

How do we monitor patients on statins – the ACC/AHA/NHBLBI Clinical Advisory on Statins

Baseline measurements including a lipid profile, AST and ALT, and CK levels are recommended according to the ACC/AHA/NHBLBI Clinical Advisory on Statins before commencing statin therapy[11].

The ATP III report and the ACC recommend baseline CK measurement since asymptomatic CK elevations are common and pre-treatment recognition of such elevated CK levels would aid clinical decisions later during follow-up of the drug's safety. Asymptomatic patients with moderate CK elevations (between 3 to 10 times ULN) at baseline can usually be treated with a statin without harm, although particularly careful monitoring is strongly advised. Expert panels do not generally recommend routine ongoing monitoring of CK levels in asymptomatic patients.

Current labeling approved by FDA also recommends baseline ALT and AST measurements, at 6 and 12 weeks after initiation of treatment or elevation in dose, and half yearly thereafter. However, some hepatobiliary experts find it debatable (as discussed above). Transaminase elevations less than 3 times ULN are not thought to be a contraindication to initiating, continuing or advancing statin therapy, although these patients should be carefully monitored. The general follow-up schedule recommended by the ACC/AHA/NHLBI clinical advisory[11] is shown in Table 2.

Use the lowest possible dose of statins

Prevention is still the best approach to managing statin-induced myopathy. The lowest dose of statins required to reach ATP III therapeutic goals should be used. Doctors may also want to consider discontinuing statins before events that will exacerbate muscle injury, such as major surgery or extremely strenuous sports like marathon running[13].

Monitoring for adverse reactions and adjusting therapy

Upon initiation of statin therapy, patients should be educated on the important side effects of the medication. Once therapy has been commenced, symptoms may appear at any time. Patients should be instructed to stop the statins and promptly report any unexpected muscle pain and weakness or urine discoloration, as many patients with rhabdomyolysis and renal failure ignored such early symptoms of myopathy. A CK measurement should be obtained if the patient reports suggestive muscle symptoms[11]. TFT should also be done in symptomatic patients to exclude hypothyroidism as a contributing factor. Doctors should not dismiss such muscle complaints, especially if accompanied by raised CK levels. Common causes of muscle soreness or pain, such as exercise or strenuous work should be ruled out if the patient has muscle symptoms. Patients on statin-fibrate combination therapy with muscle symptoms can be advised to moderate their activities.

Symptomatic patients with no or mild-moderate (3 to 10 times ULN) CK elevation can be followed up weekly for muscle symptoms and CK levels. A reduction in dose or temporary discontinuation of statin should be considered for symptomatic patients with increasing serial CK levels.

According to the ACC/AHA/NHLBI clinical advisory on the use and safety of statins[11], there is no need to stop statins in asymptomatic patients with raised CK levels less than 10 times the ULN if the physician chooses to routinely monitor CK levels (eg. for patients on combination therapy). Asymptomatic patients with moderate CK elevations (3 to 10 tomes ULN) during treatment or after a drug holiday can usually be treated with a statin without harm. The benefit of statin therapy in the patient should be re-evaluated[13]. Patients with established vascular disease or an estimated cardiovascular risk equivalent to that of patients with established disease are likely to benefit more from continuing statin therapy. However, these patients should be advised to stop statin immediately and contact their physician if they become symptomatic or notice dark-colored urine, and CK levels should be monitored.

In general, statins should be discontinued if CK level is elevated to more than ten times ULN especially if the patient has muscle complaints, although some experts recommend only "strong consideration" to stopping the medication if the patient is asymptomatic. For the asymptomatic patients on combination therapy, the ACC/AHA/NHLBI clinical advisory[11] suggests that the physician should wait till the CK levels to normalise before restarting therapy with either drug and use a lower dose if possible.

Patients complaining of myalgia without elevated CK levels can continue statins if their symptoms are tolerable. If the symptoms are intolerable or worsening, the medication should be stopped.

Table 2. Statins - Monitoring Parameters and Follow-up Schedule

Monitoring of clinical symptoms	Follow-up schedule
Muscle soreness, tenderness, or pain; muscle weakness	Evaluate muscle symptoms and CK before starting therapy. Evaluate muscle symptoms 6-12 weeks after starting therapy and at each follow-up visit. Obtain CK level when patient has muscle soreness, tenderness, or pain.
Headache, dyspepsia	Evaluate symptoms initially, 6-8 weeks after starting therapy, then at each follow-up visit
Liver transaminases (ALT, AST)	Evaluate ALT and AST initially, approximately 12 weeks after starting therapy, then annually or more frequently if indicated.

Physicians should bear in mind that the patients who are at highest risk for statin-associated myopathy are the same people who would most likely require and benefit from statin therapy. Hence, careful monitoring of these patients is advisable. The risk factors for statin-induced myopathy include advanced age, small build, women, multi-systemic disease (especially diabetes), renal and hepatic dysfunction, hypothyroidism, multiple medications especially concomitant medications which interact with statins (Table 3), and alcohol abuse[17-19].

Drug interaction is a major contributing factor for statin myopathy. However, there is no absolute contraindication to combining a statin with another agent known to increase the risk of myopathy if benefits of combined therapy are likely to outweigh the risks[11]. Combination of a statin and a fibrate or niacin is frequently required in patients with high LDL and triglycerides. The use of moderate statin dosages combined with a fibrate appears to have relatively low incidence of myopathy, especially when used in persons without multi-systemic disease or other multiple medications.

Renal transplant patients and HIV patients commonly develop hyperlipidemia from immunotherapy and anti-viral therapy respectively. These patients often require statin therapy or even a combination of statin and fibrate, even though cyclosporin and protease inhibitors are known to increase the risk of rhabdomyolysis. In such cases, the patient must understand and accept this risk, and be reminded to promptly report any suspicious symptoms.

Some experts suggest atorvastatin and pravastatin for combination therapy since these agents seem to have a low incidence of rhabdomyolysis[12,13], however available data does not permit firm conclusions. Atorvastatin and fluvastatin have minimal renal excretion, and dose adjustment of these statins in patients with renal insufficiency is therefore unnecessary[33]. Although all fibrates have been associated with myopathy when

Table 3. Summary of Statins (HMG CoA Reductase Inhibitors)

Available drugs	Lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin				
Major use	To reduce LDL-C				
Lipid/lipoprotein effects		Reduction in TC %	Reduction in LDL-C %	Increase in HDL-C %	Reduction in TG %
	Lovastatin	16 – 34	21 – 42	2 – 10	6 – 27
	Pravastatin	16 – 25	22 – 34	2 – 12	15 – 24
	Simvastatin	19 – 36	26 – 47	8 – 16	12 – 34
	Fluvastatin	16 – 27	22 – 36	3 – 11	12 – 25
	Atorvastatin	25 – 45	26 – 60	5 – 13	17 – 53
	Rosuvastatin	33 – 46	45 – 63	8 – 14	10 – 35
Contraindications:					
Absolute	Active or chronic liver disease				
Relative	Concomitant use of cyclosporine, fibrates (especially gemfibrozil) or niacin, macrolide antibiotics, anti-fungal agents, HIV protease inhibitors, verapamil, amiodarone, cytochrome P-450 inhibitors				
Other risk factors for myopathy	o Advanced age (especially >80yrs) o Women o Small body frame and frailty·Multisystemic disease (eg. CRF especially due to diabetes) o Multiple medications o Perioperative periods o Alcohol abuse (independent risk factor for myopathy and liver disease)				
Efficacy	Reduce risk for CHD and stroke (primary and secondary prevention)				
Safety	Side effects minimal in clinical trials				
Usual starting dose	Lovastatin	20mg OD			
	Pravastatin	20mg OD			
	Simvastatin	20mg OD			
	Fluvastatin	20mg OD			
	Atorvastatin	10mg OD			
	Rosuvastatin	10mg OD			
Maximum FDA-approved dose	Lovastatin	80mg OD			
	Pravastatin	80mg OD			
	Simvastatin	80mg OD			
	Fluvastatin	80mg OD			
	Atorvastatin	80mg OD			
	Rosuvastatin	40mg OD			
Available preparations	Lovastatin	10, 20,40mg tab			
	Pravastatin	10, 20, 40, 80mg tab			
	Simvastatin	5, 10, 20, 40, 80mg tab			
	Fluvastatin	20, 40, 80mg tab			
	Atorvastatin	10, 20, 40, 80mg tab			
	Rosuvastatin	5, 10, 20, 40mg tab			

used with statins, perhaps statin-fenofibrate combinations may have less risk for interactions than therapy with statins and gemfibrozil[32]. Merck & Co. has also altered its recommendations to state that simvastatin doses should not exceed 10mg/d when combined with cyclosporin or fibrates, or more than 1 g/d of niacin; or 20mg/d with concomitant verapamil and amiodarone[34].

Ezetimibe offers new hope for us. It is a new inhibitor of intestinal cholesterol absorption approved by FDA in October 2002, and can be used alone or with a statin. It produces an average additional 14% reduction in LDL when combined with a statin. To date, there is no evidence that statin-ezetimibe combination therapy increases muscle-related side effects beyond the risk associated with statin monotherapy[35-38].

CONCLUSION

The issue of statin-related myopathy must be viewed in the context of the remarkable clinical benefits that statin therapy can offer to patients. The incidence of statin-induced fatal rhabdomyolysis is low, but the frequency of the less-severe muscle complaints is not well defined. Careful patient selection, patient education, follow-up can reduce the risk of statin therapy while optimizing its benefits.

REFERENCES

1. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study. *Lancet.* 1994;334:1383-9.
2. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med.* 1998;339:489-97.
3. Sacks FM, Pfeffer MA, Moye LA. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med.* 1996; 335:1001-9.
4. Collins R. Results of the Heart Protection Study (HPS). Presented at: 2001 American Heart Association Scientific Sessions; Nov 2001.
5. Shepherd J, Cobbe SM, Ford I, et al, for the West Scotland Coronary Presention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. *N Engl J Med.* 1995;333:1301-7.
6. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS: Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA*. 1998;279:1615-22.
7. LaRossa JC, He J, Vupputuri S. Effects of statins on risk of coronary disease: a meta-analysis of randomised controlled trials. *JAMA.* 1999;282:2340-6.
8. Serruys PWJC, de Feyter P, Macaya C, et al. Fluvastatin for prevention of cardiac events following first percutaneous coronary intervention: a randomised controlled trial. *JAMA*. 2002;287:3215-22.
9. NCEP Expert Panel. Executive summary of the third report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high Blood cholesterol in adults (Adult Treatment Panel III) JAMA 2001; 285:2486-897.
10. Grundy SM, Cleeman JI, Bairey MN, et al. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation.* 2004; 110:227-39.
11. Pasternak RC, Smith SC, Bailey-Merz CN, et al. ACC/AHA/NHLBI Clinical advisory on the use and safety of statins. *J Am Coll Cardio.* 2002: 40:567-72.
12. Staffa JA, Chang J, Green L. Cerivastatin and reports of fatal rhabdomyolysis. *N Engl J Med.* 2002;346:539-40.
13. Thompson PD, Clarkson P, Karas RH. Statin-associated myopathy. *JAMA.* 2003;289:1681-90.
14. Herman RJ. Drug interactions and the statins. *CMAJ.* 1999; 161: 1281-6.
15. Knochel JP. Catastrophic medical events with exhaustive exercise: "white collar rhabdomyolysis". *Kidney Int.* 1990;38:709-19.
16. Ballantyne CM, Corsini A, Davidson MH, et al. Risk for myopathy with statin therapy in high-risk patients. *Arch Intern Med*. 2003;163:553-64.
17. Goldman JA, Fishman AB, et al. The role of cholesterol-lowering agents in drug-induced rhabdomyolysis and polymyositis. *Arthritis Rheum*. 1989;32:358-9.
18. Wanner C, Kramer-Guth A, Galle J. Use of HMG CoA reductase inhibitors after kidney and heart transplantation: lipid-lowering and immunosuppressive effects. *BioDrugs.* 1997;8:387-93.
19. Hanston PD, Horn JR. Drug interactions with HMG CoA reductase inhibitors. *Drug Interactions Newsletter*. 1998:103-6.
20. Ucar M, Mjorndal T, Dahlqvist R. HMG CoA reductase inhibitors and myotoxicity. *Drug Saf.* 2000;22:441-57.
21. Hamilton-Craig I. Statin-associated myopathy. *Med J Aust.* 2001;175:486-9.
22. Bradford RH, Shear CL, Chremos AN, et al. Expanded clinical evaluation of lovastatin (EXCEL) study results. Arch Intern Med. 1991;151:43-9.
23. *Physicians' Desk Reference*. 56th ed. Montvale, NJ: Medical Economics; 2002.
24. Phillips PS, Haas RH. Statin-associated myopathy with normal creatine kinase levels. *Ann of Intl Med*. 2003;138:1008-9.
25. Walravens PA, Greene C, Frerman FE. Lovastatin, isoprenes and myopathy. Lancet. 1989;2:1097-8.
26. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high risk individuals:a randomised placebo-controlled trial. *Lancet*. 2002;360:7-22.
27. Sniderman AD. Is there value in liver function test and creatine phosphokinase monitoring with statin use? *Am J Cardio* 2004; 94:30F-34F.
28. Tolman KG. The liver and lovastatin. *Am J Cardio* 2002; 89:1174-80.
29. Angulo P. Nonalcoholic fatty liver disease. *N Engl J Med*. 2002;346:1221-31.
30. Dujovne CA. Side effects of statins: hepatitis versus "transaminitis" – myositis versus "CPKitis". *Am J Cardio* 2002; 89:1411-3.
31. Gotto AM. Safety and statin therapy: Reconsidering the risks and benefits. *Arch Int Med* 2003;163:657-9.
32. Vaughan CJ, Gotto AM. Update on statins: 2003. *Circulation* 2004; 110:886-92.
33. Omar MA, Wilson JP, Cox TS. Rhabdomyolysis and HMG-CoA reductase inhibitors. *Ann Pharmacother*. 2001;35:1096-107.
34. Physicians' Desk Reference. Vol 57. Montvale, NJ: Thomson;2003:2126-31.
35. Gagne C, Bays HE, Weiss SR, et al. Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. *Am J Coll Cardio*. 2002;90:1084-91.
36. Davidson MH, McGarry T, Bettis R, et al. Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. *J Am Coll Cardio*. 2002;40:2125-34.
37. Ballantyne CM, Houri J, Notarbartolo A, et al. Effect of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomised, double-blind trial. *Circulation*. 2003;107:2409-15.
38. Kerzner B, Corbelli J, Sharp S, et al. Efficacy and safety of ezetimibe coadministered with lovastatin in primary hypercholesterolemia. *Am J Cardio*. 2003;91:418-24.