ADJUVANT THERAPY FOR CARDIOVASCULAR HEALTH

Statins for All Patients with Hypertension— It is still not Prime Time!

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ABSTRACT

The hydroxymethylglutaryl (HMG) coenzyme A (CoA) reductase inhibitors (popularly known as statins) are very widely used drugs for the secondary and the primary prevention of cardiovascular (CV) events. Many medical societies have enthusiastically been updating their recommendations as the new evidences emerge. Considering statins routinely for all patients who are diagnosed to have systemic hypertension is possibly not prudent considering the currently available data. It is not uncommon that a person is diagnosed to have hypertension in thirties and forties. Although exposing him to statins on a very long term may have certain advantages such as prevention of CV events, it is well known that the residual risks in statin trials have been very significant. Moreover, militating against this suggestion is the lifetime risk of side effects and costs of therapies even when one chooses "more economical" statins. In the interim, clinical judgment on the merits of the case after a thorough discussion between care giver and seeker is reasonable.

Keywords: HMG-CoA reductase inhibitors, Hypertension, Primary prevention, Statins.

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INTRODUCTION

The role of pharmacological lipid-lowering interventions in individuals with dyslipidemia and cardiovascular disease (CVD) or diabetes/chronic kidney disease (CKD) has been well established. Recommendations for immediate initiation of drugs along with lifestyle intervention in patients at a high or very high cardiovascular (CV) risk have been propounded by the European Society of Cardiology guidelines. The approach should have the potential of providing the long-sought

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individualized approach to CVD management based on 21st century testing that could replace the population-based risk factor approach that characterized the 20th century. Statins would generally be the first-choice drug intervention, given the robust evidence of reduction in all-cause mortality and major adverse cardiac events (MACEs). Recent observational studies looking forward at substantially decreasing the burden of CVD and mortality such as the coronary artery risk development in young adults (CARDIA) study have suggested lowering low-density lipoprotein (LDL)-cholesterol earlier in life and for a longer duration can achieve this goal rather than initiating interventions later in life.[1]

Results from recent well-conducted large meta-analyses of randomized clinical trials have shown reduced all-cause mortality by 14% and MACE by >20% for primary prevention with the use of statins, similar to the usage of statins for secondary prevention.[2] We aim in this review to discuss the data that advocate the use of statins in primary prevention especially in the context of hypertensive individuals, putting the efficacy evidence into perspective with new insights in terms of safety issues. Hypertension being a very common disorder and risk factor for coronary and other vascular syndromes, the preventive strategies would ideally have to be all-encompassing. Adding statin to the prescription of a hypertensive patient routinely entails huge expenditure at the population level. Rightly, such an issue requires continuous examination. Hence, it is appropriate to evaluate this.

Ischemic heart disease and stroke continue to be the leading causes of death worldwide, with a trend to increase in rates as compared with the last decade and are still ranked the first and second causes of death worldwide. Approximately 25% of the deaths worldwide are due to the two diseases combined.[3] Worldwide, dynamics of death rates attributable to CVDs has been different in different geographical locales. In the USA, an opposite trend was observed, with declining rates of death attributable to CVDs in the past decade.[4] Although death rates due to CVDs are on a decline,[4] they still account for one-third of the deaths in the USA. Similar trends have been seen in Europe,[5] with deaths due to CVD and coronary heart disease (CHD), accounting for 46% and 20% of deaths, respectively. However, substantial inequalities are

observed between the countries.[3] The overall prevalence of hypertension in India is about 28%.[6] Given the burden of the problem, though exact data from our country are lacking, it may be extrapolated that the burden of CHD and cerebrovascular disease would be alarming.

Regarding the LDL-cholesterol levels, data from the French MONICA registry have shown that treatment with statins in primary prevention can change the initial presentation of acute coronary syndrome (ACS), with more non-ST-segment elevation myocardial infarction (MI) and unstable angina and less ST-segment elevation MI[7] in comparison with patients not treated with statins before the first manifestation of acute CHD.

Primary Prevention with Statins

Although there has been a marked improvement in awareness and treatment of hypertension, the adoption of lipid-lowering therapies seems to lag behind in a substantial proportion of patients with hypercholesterolemia and comorbidities. In the USA, approximately 60% of diabetic individuals do not receive a lipid-lowering agent,[8] and in patients with CKD, fewer than one-third receive lipid-lowering drugs and only 40% are at LDL-C goal.[9] In Europe, encouraging trends toward a decrease in mean LDL-C concentrations have been observed,[10,11] but LDL-C management has been worryingly suboptimal in high-risk groups as in the French MONALISA study,[12] wherein only 42% of patients at a high or very high risk, according to the latest European guidelines,[13] received lipid-lowering therapy. As per the MONALISA study, although a slight majority of patients at a very high risk (58%) actually benefit from a lipid-lowering agent, the vast majority (72%) of those eligible for primary prevention (high-risk group with multiple comorbidities but no CVD) are excluded from the recommended therapy.[12] Overall, the key findings of observational studies suggest that the management of high LDL-C is particularly limited to highest risk groups for primary prevention compared with those treated for secondary prevention and lower-risk groups.

An important trial looking at lipid lowering in hypertensive individuals was the the lipid lowering trial component of the Antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT-LLT).[13] This was a multicenter randomized trial comparing usual care *vs* treatment with a statin in moderate hypercholesterolemia treated hypertensive cohort with other CHD risk factors, including preexisting CVD.[14]

The results of this trial were in stark contrast to those of other statin trials,[15] which were attributable to the treatment crossovers and a consequently smaller than expected differential reduction in cholesterol levels. There was no difference in the primary endpoint of all-cause mortality [hazard ratio (HR) 0.99; 95% confidence interval (95% CI), 0.89–1.11; p = 0.88], and a nonsignificant lowering of secondary CHD endpoints of CHD death (HR 0.91; 95% CI, 0.79–1.04; p = 0.16) and nonfatal MI after an average of 4.8 years of follow-up.[16] Also, fatal and nonfatal stroke was nonsignificantly reduced in the pravastatin group (HR 0.91; 95% CI, 0.75–1.09; p = 0.31).

There was no heterogeneity of ALLHAT-LLT primary and secondary outcomes by age, sex, previous history of CHD, history of diabetes, or baseline level of cholesterol.[16] However, significant racial differences were observed for secondary outcomes of CHD and stroke. For stroke, pravastatin showed no benefit in blacks but was protective in nonblacks (HR 1.12; 95% CI 0.86–1.48 *vs* 0.74; 95% CI 0.57–0.96; p for interaction = 0.03), whereas for CHD events, pravastatin was protective in blacks but not in nonblacks (HR 0.71; 95% CI 0.57–0.90; p = 0.005 *vs* 1.00; 95% CI 0.85–1.19; p = 0.095, p for interaction = 0.02).[17] These differences were not accounted for by baseline differences in risk factors, adherence during trial, or achieved blood pressure (BP) and lipid lowering.[17]

Another landmark trial from the UK, the Anglo-Scandinavian Cardiac Outcomes Trial-lipid-lowering arm (ASCOT-LLA), was an offshoot of the ASCOT-blood pressure lowering arm (ASCOT-BPLA).[18]

Anglo-scandinavian cardiac outcomes trial-lipid-lowering arm was a factorially designed, double-blind, placebo-controlled trial of atorvastatin in 10,305 hypertensive patients enrolled into the ASCOT-blood pressure lowering arm (BPLA) of the trial and with total cholesterol concentrations, at baseline, of <6.5 mmol/l. ASCOT-LLA was prematurely stopped after a median 3.3-year follow-up, as there was a 36% relative risk reduction (RRR) in the primary outcome, that is, nonfatal MI and fatal CHD in favor of atorvastatin and a nonsignificant reduction in CV deaths (16%) and all-cause mortality (13%). Despite extensive crossovers from and to statin usage, the RRR in all endpoints remained essentially unchanged after a further 2.2 years at the end of ASCOT-BPLA. A median 11 years after initial randomization and ~8 years after closure of LLA, all-cause mortality (n = 520 and 460 in placebo and atorvastatin, respectively) remained significantly lower in those originally assigned to atorvastatin (HR 0.86, 95% CI, 0.76–0.98, p = 0.02). Cardiovascular deaths were fewer, but not significant (HR 0.89, 95% CI 0.72–1.11, p = 0.32).[18]

A meta-analysis of 3,12,321 participants estimated the clinical benefit of lowering LDL early in life where the authors used inherited allocation to protective genotypes (for nine single-nucleotide polymorphisms associated with lower LDL-C) as a proxy for a treatment that would decrease LDL-C beginning at birth. Results showed that a low LDL-C concentration following this random natural allocation decreases the risk of CHD by 54.5% for each

mmol/l decrease in LDL-C. In contrast, for the same level of decrease in LDL-C, statin therapy started later in life would reduce the risk of CHD by only 24%.[19] Long-term exposure to a protective lower LDL-C beginning early in life was associated with a greater reduction in the risk of CHD than the current practice of starting to lower LDL-C later in life.

The deleterious effect of early and long-term exposure to dyslipidemia was studied in the CARDIA study.[1] The effect of time-averaged cumulative exposure to dyslipidemia starting in young adulthood (healthy subjects at enrolment, aged 18–30 years) was assessed over a 20-year period in 3258 participants and related to coronary calcium levels measured later in life. Sixty-five percent of the patients were exposed to LDL-C concentrations > 100 mg/dl. Exposure to high LDL-C concentrations was strongly associated with coronary calcium later in life, compared with subjects with optimal LDL-C concentrations <70 mg/dl.

Hypertension *per se* in itself can predispose to coronary and cerebrovascular events. Given a compounding milieu of dyslipidemia, increased plaque burden and vulnerable plaques would definitely be counterproductive in coercion. Uncontrolled hypertension can, by shearing stress, rupture unstable plaques and thence leading to catastrophic complications, especially in the coronary and cerebrovascular beds. Hence, optimal treatment of hypertension should address optimal holistic lipid management also.

Patients with no Known CV Disease

Treating patients with hypertension and other CV risk factors but no known CVD would translate to fewer deaths, longer survival times, and less fatal and nonfatal CVD, such as MI and stroke (Table 1).[20]

The magnitude of risk reduction for CVD is similar for treatment with antihypertensive or lipid-lowering

Table 1: Magnitude of risk reduction in hypertensive individuals with no known cardiovascular disease with different treatment strategies

Treatment	Approximate change (%) in relative risk (range)	
	Death	Cardiovascular diseases
Angiotensin–converting enzyme inhibitor	−15 (−25 to −5)	−20 (−30 to −15)
Antiglycemic drugs	Not shown	Not shown
Antihypertensive drugs	10 (5 to −10)	−30 (−40 to −15)
Antilipidemic drugs	−5 (−20 to 15)	−30 (−40 to −20)
Aspirin	−5 (−15 to 5)	−15 (−30 to −5)
Physical activity	Unclear	Unclear
Smoking cessation	Unclear ≥ −20	Unclear ≤ −50

Table 2: Magnitude of risk reduction in hypertensive individuals with no known cardiovascular disease and with different treatment strategies

Treatment	Approximate change (%) in relative risk (range)	
	Death	Cardiovascular diseases
Angiotensin–converting enzyme inhibitor	−15 (−25 to −5)	−20 (−30 to −15)
Antiglycemic drugs	Not shown	Not shown
Antilipidemic drugs	−20 (−30 to −10)	−30 (−40 to −20)
Aspirin	−15 (−20 to −10)	−25 (−40 to −10)
β-blockers	−25 (−30 to −15)	−25 (−40 to −10)
Cardiac rehabilitation	−25 (−40 to −10)	−25 (−40 to −10)
Fish oil	−15 (−25 to −5)	−10 (−20 to 0)
Mediterranean diet	−30 (−80 to −10)	−30 (−85 to −45)
Smoking cessation	Unclear ≥ −20	Unclear ≤ −50

drugs. Aspirin prophylaxis has a slightly lower role. Both the type and magnitude of benefits that can be expected from lifestyle modifications, such as exercising more or quitting smoking, are less clear. Some treatments, such as aspirin, are immediately beneficial, while others, such as lipid lowering, may take a long time to take effect.

Patients with Known CV Disease

Patients with hypertension and known CVD are at a high risk of future CV events and warrant aggressive management of their risk factors (Table 2).[20]

Adverse Effects (AEs) of Statin Therapy

Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) have been one of the best selling prescription drug class worldwide. Hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are thought to have a favorable safety profile[21,22] and are well documented to benefit CVD in many groups across the age groups and genders who are at a high risk.

No drug is without potential AEs and statins are no exception. Although many people treated with statins do well, the treating physician needs to be well aware of the risks and benefits of all drugs, particularly those, such as statins, that are used on a wide scale where, though uncommon, adverse drug effects can translate to significant public health impact. Statins inhibit the enzyme HMG-CoA reductase in the mevalonate pathway, at an early stage.[23] This pathway is involved in other products in addition to cholesterol, heme-A, such as coenzyme Q10, and isoprenylated proteins.[23] These have pivotal roles in physiology and potential relevance to the risks and benefits of the drug.[24,25] Cholesterol itself is not merely a final product but also an intermediate substrate to a myriad of additional products of fundamental relevance

to health and disease, such as sex steroids, corticosteroids, bile acids, and vitamin D, some of which may potentially be affected with the use of statins.[26,27] The biochemical influences of statins are not limited to the lipid profile and its constituents and even beyond the direct products of the mevalonate pathway. This includes a wide variety of products and functions modified through these as well as nonmevalonate products of statins such as nitric oxide and inflammatory markers,[28] polyunsaturated fatty acids,[29] among many others.

Dose-dependent reductions in coenzyme Q10,[30] induced by statins, may lead to a key mitochondrial antioxidant and electron transport carrier that serves to help bypass existing mitochondrial respiratory chain defects.[30] Hence, mitochondrial dysfunction may underlie additional AEs reported on statins.[31]

Muscle AEs

Adverse Effects in the muscle such as myositis and myalgia are the best recognized and commonly reported AEs of statins.[32] They can range across a spectrum from muscle pain to fatigue and weakness to rhabdomyolysis.[33] Moreover, studies have also inferred that these effects may not fully normalize with discontinuation of statin therapy. Myositis has been classically defined as creatinine kinase (CK) > 10 times the upper limit of normal with myalgia.[34] Although individual randomized controlled trials (RCTs) often fail to show significant muscle problems or symptoms, a meta-analysis of randomized, double-blind, placebo-controlled trials has shown an increased myositis in patients receiving statins. [odds ratio (OR) 2.56, 95% CI 1.12–5.85]. A meta-analysis of RCTs that compared statins with placebo did not find myalgia to be increased [relative risk (RR) 1.09, 95% CI 0.97–1.23],[34] but this does not necessarily mean that statins do not cause myalgia. In stark contrast to the above findings, evidence has shown that statins can reduce pain and improve walking distance in many individuals, for instance, in persons with peripheral arterial disease.[35] This effect is possibly due to improvement in endothelial function and blood flow in those with dysfunction.[36] Partially reversible mitochondrial myopathy may also be observed with non-CK-elevating or minimally CK-elevating muscle symptoms on statins.[37] In a family in which multiple members experienced statin-associated non-CK elevating muscle pain, objective investigation affirmed myopathic findings.[38] Prior muscle symptoms on statins may predict future symptoms with statin rechallenge and also predict a risk for rhabdomyolysis.[39–41] Rhabdomyolysis is one of the best-recognized and most feared complication of statins.[33] Profound muscle damage with marked elevation of CK (more than 10 times the upper limit of

normal) is often accompanied by evidence of renal dysfunction.[42,43] In fact, cerivastatin was withdrawn from the market due to excess risk of rhabdomyolysis, particularly in combination with fibrates (and specifically gemfibrozil),[44,45] although no cases of rhabdomyolysis occurred on cerivastatin in a meta-analysis of randomized trials.[34] Renal failure is well recognized and is a consequence of the rhabdomyolysis, but concurrent heart, pancreas, liver, bone marrow, respiratory, and central nervous system (CNS) toxicity or all of the above[46] are also reported. These AEs may not be entirely dose dependent, though dose-relation has been observed more frequently.[47] Concurrent use of drugs that inhibit metabolic pathways of statins, compete for metabolism with statins, or cause similar or interacting toxicity may worsen the AEs. Most of the statins—atorvastatin, simvastatin, and lovastatin (and previously cerivastatin)—are metabolized by the cytochrome P450 (CYP)3A4 pathway.[48] Pravastatin and rosuvastatin are not metabolized by these systems.[48] Concurrent administration of statins with CYP3A4 inhibitors such as cyclosporin, erythromycin, ketoconazole antifungals, and antiretrovirals such as ritonavir[48] may increase serum statin concentrations and risk of toxicity, including rhabdomyolysis.[49] Some agents such as calcium channel blockers are weaker CYP3A4 inhibitors and may increase statin rhabdomyolysis risk, though the risk is minimal.[48]

Muscle is highly aerobically dependent and selectively vulnerable to mitochondrial pathology.[30] Hence, mitochondrial mechanisms have been repeatedly implicated in muscle AEs of statins. Mitochondrial defects predispose to problems due to statins as well as statins predispose to mitochondrial defects in vulnerable individuals.[37] Reductions in coenzyme Q10 in a dose-dependent manner[30] can reduce cellular energy production, promote oxidation, promote apoptosis, and unmask silent mitochondrial defects.[50] Additional products of the mevalonate pathway such as heme-A, which has its own central involvement in mitochondrial electron transport, are also inhibited by statin use.

Nonmuscle AEs

Mitochondrial mechanisms may also be involved in a range of nonmuscle statin AEs. Failure of other organs may be isolated or most often in concert with multiple organ dysfunction *vis-a-vis* rhabdomyolysis in the context of statin rhabdomyolysis.[42] The brain, with only about 2% to 4% of (nonobese) body mass utilizes approximately 20% of oxygen and 50% of glucose.[51] Brain grey matter has a high mitochondrial vulnerability as muscle tissue due to high metabolic demand.[51] Cognitive problems are second only to muscle problems among patient reports of statin AEs.[52,53] Classically, mitochondrial diseases such

as mitochondrial myopathy and encephalomyopathy classically involve the muscle and the brain as with statin use. Gastrointestinal and neurological symptoms, psychiatric symptoms, sleep problems, glucose elevations, and a range of other symptoms reported on statins also arise in mitochondrial dysfunction.[33]

Elevation of Liver Enzymes

Treatment with statins tends to increase hepatic transaminases in a dose-dependent manner. Meta-analyses of randomized placebo controlled trials have demonstrated that low to moderate doses of statins may not be associated with clinically significant elevations in transaminases (>3 × upper limit of normal).[54,55] However, maximal doses of all statins may be associated with a modest but significant elevation of transaminase levels.[55,56] Many guidelines had been recommending to monitor liver enzymes before statin treatment and regularly during treatment.[57] The National Lipid Association Statin Safety Task Force in 2006 published an assessment of statin safety as well as conclusions and recommendations.[58,59] As per the observations of the task force, significant liver disease caused by the statin treatment is extremely uncommon and elevation of liver enzymes is self-limiting with continued therapy; the US foods and drugs administration (FDA) in 2012 changed its recommendation. Hepatic function test is now recommended to be performed before starting therapy and as clinically indicated thereafter, not as a routine monitoring[60] with special attention directed toward clinical symptoms in patients with an increased risk for statin-related side effects. Also, the presence of nonalcoholic fatty liver disease should not be considered a contraindication to statin therapy.[61-63]

New-onset Diabetes Mellitus and worsening Sugars

Statins can modestly raise blood sugars as evidenced by several trials, and several of these patients who are on statins are already diabetic. Although patients on statins experience a significant drop in CV events, they do have a higher risk of developing diabetes mellitus. In a study, diabetes mellitus was diagnosed in 27% more patients receiving a statin (rosuvastatin) than placebo.[64] The findings do show that new-onset diabetes mellitus is more common in the patients who received statin treatment. A meta-analysis of 13 individual studies (involving a total of 91,140 patients) showed that treating 255 patients with statins for at least 4 years showed one case of new onset diabetes mellitus, whereas 5.4 CV events were prevented.[65] The effect of statins on glucose are small, and the development of new-onset diabetes mellitus

or worsening of diabetes mellitus may be negligible. In patients without diabetes mellitus, fasting sugars are increased by 3 mg/dl and increased hemoglobin A1c by about 0.3%[66] for patients using statins compared with those who were not. Thus, whereas there is an effect of statins on glycemia, the exacerbation of diabetes mellitus though relatively meager is still a possibility, but given the CV protection provided the potential risk if any may be clinically unimportant in a given patient. However, this biological signal warrants further evaluation in future studies.

CONCLUSION

Statins, in general, are considered powerful molecules to reduce CV events. Although statins are being proposed to be a linchpin of current approaches to CV protection, AEs of statins are neither rare nor of trivial clinical importance. The risk–benefit balance of treatment, including economics of therapy, should be carefully assessed. The onus is on the clinician in weighing the pros and cons of statin therapy in a patient with hypertension. Currently, it may not be imperative for universal recommendation of statins for all hypertensive individuals, given the side effect profile and economic implications.

REFERENCES

1. Pletcher MJ, Bibbins-Domingo K, Liu K, Sidney S, Lin F, Vittinghoff E, Hulley SB. Non optimal lipids commonly present in young adults and coronary calcium later in life: the coronary artery risk development in young adults (CARDIA) study. Ann Intern Med 2010 Aug3;153(3):137-146.
2. Taylor FC, Huffman M, Ebrahim S. Statin therapy for primary prevention of cardiovascular disease. JAMA 2013 Dec11;310(22):2451-2452.
3. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990and 2010: a systematic analysis for the global burden of disease study 2010. Lancet 2012 Dec 15;380(9859): 2095-2128.
4. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ, Dai S, Ford ES, Fox CS, Franco S, et al. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. Circulation 2014 Jan1;127(1): e6-e245.
5. Nichols M, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe: epidemiological update. Eur Heart J 2013 Oct;34(39):3028-3034.
6. Zachariah MG, Thankappan KR, Alex SC, Sarma PS, Vasan RS. Prevalence, correlates, awareness, treatment, and control of hypertension in a middle-aged urban population in Kerala. Ind Heart J 2003 May-Jun;55(3):245-251.
7. Vervueren PL, Elbaz M, Dallongeville J, Arveiler D, Ruidavets JB, Montaye M, Wagner A, Amouyel P, Haas B, Bongard V, et al. Relationships between chronic use of statin therapy, presentation of acute coronary syndromes and one-year

mortality after an incident acute coronary event. Int J Cardiol 2013 Feb10;163(1):102-104.

8. Kuznik A, Mardekian J. Trends in utilization of lipid- and blood pressure-lowering agents and goal attainment among the US diabetic population, 1999—2008. Cardiovasc Diabetol 2011 Apr 17;10:31.

9. Kuznik A, Mardekian J, Tarasenko L. Evaluation of cardiovascular disease burden and therapeutic goal attainment in US adults with chronic kidney disease: an analysis of national health and nutritional examination survey data, 2001–2010. BMC Nephrol 2013 Jun27;14:132.

10. Eliasson M, Janlert U, Jansson JH, Stegmayr B. Time trends in population cholesterol levels 1986–2004: influence of lipid-lowering drugs, obesity, smoking and educational level. The northern Sweden MONICA study. J Intern Med 2006 Dec;260(6):551-559.

11. Ferrieres J, Bongard V, Dallongeville J, Arveiler D, Cottel D, Haas B, Wagner A, Amouyel P, Ruidavets JB. Trends in plasma lipids, lipoproteins and dyslipidaemias in French adults, 1996–2007. Arch Cardiovasc Dis 2009 Apr;102(4):293-301.

12. Bongard V, Dallongeville J, Arveiler D, Ruidavets JB, Amouyel P, Wagner A, Ferrieres J. Attainment of low-density lipoprotein cholesterol target in the French general population according to levels of cardiovascular risk: insights from the MONALISA study. Arch Cardiovasc Dis 2013 Feb;106(2):93-102.

13. Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J 2011 Jul;32(14):1769-1818.

14. Margolis KL, Davis BR, Baimbridge C, Ciocon JO, Cuyjet AB, Dart RA, Einhorn PT, Ford CE, Gordon D, Hartney TJ, et al. ALLHAT Collaborative Research Group Long-term follow-up of moderately hypercholesterolemic hypertensive patients following randomization to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). J Clin Hypertens (Greenwich) 2013 Aug;15(8):542-554.

15. Davis BR, Cutler JA, Gordon DJ, Gordon DJ, Furberg CD, Wright JT Jr, Cushman WC, Grimm RH, LaRosa J, Whelton PK, et al. Rationale and design for the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Am J Hypertens 1996 Apr;9(4 Pt 1):342-360.

16. Baigent C, Landray M, Leaper C, Altmann P, Armitage J, Baxter A, Cairns HS, Collins R, Foley RN, Frighi V, et al. First United Kingdom heart and renal protection (UK-HARP-I) study: biochemical efficacy and safety of simvastatin and safety of low-dose aspirin in chronic kidney disease. Am J Kidney Dis 2005 Mar;45(3):473-484.

17. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major outcomes in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin vs usual care: the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT). JAMA 2002 Dec 18;288(23):2998-3007.

18. Margolis KL, Dunn K, Simpson LM, Ford CE, Williamson JD, Gordon DJ, Einhorn PT, Probstfield JL. Coronary heart disease in moderately hypercholesterolemic, hypertensive black and non-black patients randomized to pravastatin versus usual care: the antihypertensive and lipid-lowering

treatment to prevent heart attack trial (ALLHAT-LLT). Am Heart J 2009 Dec;158(6):948-955.

19. Sever PS, Chang CL, Gupta AK, Whitehouse A, Poulter NR; ASCOT Investigators. The Anglo-Scandinavian Cardiac Outcomes Trial: 11-year mortality follow-up of the lipid-lowering arm in the U.K. Eur Heart J 2011 Oct;32(20): 2525-2532.

20. Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, et al. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J 2011 Jul;32(14):1769-1818.

21. Ference BA, Yoo W, Alesh I, Mahajan N, Mirowska KK, Mewada A, Kahn J, Afonso L, Williams KA Sr, Flack JM. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. J Am Coll Cardiol 2012 Dec25;60(25):2631-2639.

22. Pignone M, Mulrow CD. Evidence based management of hypertension: using cardiovascular risk profiles to individualise hypertensive treatment. BMJ 2001 May 12;322(7295): 1164-1166.

23. Davidson MH. Safety profiles for the HMG-CoA reductase inhibitors: treatment and trust. Drugs 2001;61(2):197-206.

24. Bernini F, Poli A, Paoletti R. Safety of HMG-CoA reductase inhibitors: focus on atorvastatin. Cardiovasc Drugs Ther 2001;15(3):211-218.

25. Buhaescu I, Izzedine H. Mevalonate pathway: a review of clinical and therapeutical implications. Clin Biochem 2007 Jun;40(9-10):575-584.

26. Goldstein JL, Brown MS. Regulation of the mevalonate pathway. Nature 1990 Feb 1;343(6257):425-430.

27. Mach F. Statins as immunomodulatory agents. Circulation 2004 Jun 1;109(21 Suppl 1):II15-II17.

28. Mol MJ, Stalenhoef AF, Stuyt PM, Hermus AR, Demacker PN, Van TLA. Effects of inhibition of cholesterol synthesis by simvastatin on the production of adrenocortical steroid hormones and ACTH. Clin Endocrinol (Oxf) 1989 Dec;31(6):679-689.

29. Hyyppa MT, Kronholm E, Virtanen A, Leino A, Jula A. Does simvastatin affect mood and steroid hormone levels in hypercholesterolemic men? A randomized double-blind trial. Psychoneuroendocrinology 2003 Feb;28(2):181-194.

30. Cimino M, Gelosa P, Gianella A, Nobili E, Tremoli E, Sironi L. Statins: multiple mechanisms of action in the ischemic brain. Neuroscientist 2007 Jun;13(3):208-213.

31. Harris JI, Hibbeln JR, Mackey RH, Muldoon MF. Statin treatment alters serum n-3 and n-6 fatty acids in hypercholesterolemic patients. Prostaglandins Leukot Essent Fatty Acids 2004 Oct;71(4):263-269.

32. Rundek T, Naini A, Sacco R, Coates K, DiMauro S. Atorvastatin decreases the coenzyme Q10 level in the blood of patients at risk for cardiovascular disease and stroke. Arch Neurol 2004 Jun;61(6):889-892.

33. Golomb BA, Evans MA. Statin adverse effects: a review of the literature and evidence for a mitochondrial mechanism. Am J Cardiovasc Drugs 2008;8(6):373-418.

34. Wierzbicki AS, Lumb PJ, Semra Y, Chik G, Christ ER, Crook MA. Atorvastatin compared with simvastatin-based therapies in the management of severe familial hyperlipidaemias. QJM 1999 Jul;92(7):387-394.

35. Vladutiu GD, Simmons Z, Isackson PJ, Tarnopolsky M, Peltier WL, Barboi AC, Sripathi N, Wortmann RL, Phillips PS. Genetic risk factors associated with lipid-lowering drug-induced myopathies. Muscle Nerve 2006 Aug;34(2):153-162.

36. McClure DL, Valuck RJ, Glanz M, Hokanson JE. Systematic review and meta-analysis of clinically relevant adverse events from HMG CoA reductase inhibitor trials worldwide from 1982 to present. Pharmacoepidemiol Drug Saf 2007 Feb;16(2):132-143.

37. McDermott MM, Guralnik JM, Greenland P, Pearce WH, Criqui MH, Liu K, Taylor L, Chan C, Sharma L, et al. Statin use and leg functioning in patients with and without lower-extremity peripheral arterial disease. Circulation 2003 Feb 11;107(5):757-761.

38. Arnaud C, Mach F. Pleiotropic effects of statins in atherosclerosis: role on endothelial function, inflammation and immunomodulation. Arch Mal Coeur Vaiss 2005 Jun;98(6):661-666.

39. Phillips PS, Haas RH, Bannykh S, Hathaway S, Gray NL, Kimura BJ, Vladutiu GD, England JD. Scripps Mercy Clinical Research Center. Statin-associated myopathy with normal creatine kinase levels. Ann Intern Med 2002 Oct 1;137(7): 581-585.

40. Troseid M, Henriksen OA, Lindal S. Statin-associated myopathy with normal creatine kinase levels. Case report from a Norwegian family. APMIS 2005 Sep;113(9):635-637.

41. Bruckert E, Hayem G, Dejager S, Yau C, Begaud B. Mild to moderate muscular symptoms with high dosage statin therapy in hyperlipidemic patients—the PRIMO study. Cardiovasc Drugs Ther 2005 Dec;19(6):403-414.

42. Franc S, Bruckert E, Giral P, Turpin G. Rhabdomyolysis in patients with preexisting myopathy, treated with antilipemic agents. Presse Med 1997 Dec 6;26(38):1855-1858.

43. Eriksson M, Angelin B, Sjoberg S. Risk for fatal statin-induced rhabdomyolysis as a consequence of misinterpretation of 'evidence-based medicine'. J Intern Med 2005 Mar;257(3): 313-314.

44. Antons KA, Williams CD, Baker SK, Phillips PS. Clinical perspectives of statin-induced rhabdomyolysis. Am J Med 2006 May;119(5):400-409.

45. Cziraky MJ, Willey VJ, McKenney JM, Kamat SA, Fisher MD, Guyton JR, Jacobson TA, Davidson MH. Statin safety: an assessment using an administrative claims database. Am J Cardiol 2006 Apr 17;97(8A):61C-68C.

46. Graham DJ, Staffa JA, Shatin D, Andrade SE, Schech SD, La Grenade L, Gurwitz JH, Chan KA, Goodman MJ, Platt R. Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA 2004 Dec 1;292(21): 2585-2590.

47. Su M, Hoffman RS, Flomenbaum M. Cerivastatin and gemfibrozil-induced cardiac rhabdomyolysis. Am J Forensic Med Pathol 2002 Sep;23(3):305-306.

48. Silva M, Matthews ML, Jarvis C, Nolan NM, Belliveau P, Malloy M, Gandhi P. Meta-analysis of drug-induced adverse events associated with intensive-dose statin therapy. Clin Ther 2007 Feb;29(2):253-260.

49. Neuvonen PJ, Niemi M, Backman JT. Drug interactions with lipid-lowering drugs: mechanisms and clinical relevance. Clin Pharmacol Ther 2006 Dec;80(6):565-581.

50. Lenaz G, D'Aurelio M, Merlo Pich M, Genova ML, Ventura B, Bovina C, Formiggini G, Parenti Castelli G. Mitochondrial bioenergetics in aging. Biochim Biophys Acta 2000 Aug 15;1459(2-3):397-404.

51. Fehm HL, Kern W, Peters A. The selfish brain: competition for energy resources. Prog Brain Res 2006;153:129-140.

52. de Denus S, Spinler SA, Miller K, Peterson AM. Statins and liver toxicity: a meta-analysis. Pharmacotherapy 2004 May;24(5):584-591.

53. Wlodarczyk J, Sullivan D, Smith M. Comparison of benefits and risks of rosuvastatin versus atorvastatin from a meta-analysis of head-to-head randomized controlled trials. Am J Cardiol 2008 Dec 15;102(12):1654-1662.

54. Bradford RH, Shear CL, Chremos AN, Dujovne CA, Franklin FA, Grillo RB, Higgins J, Langendorfer A, Pool JL, et al. Expanded Clinical Evaluation of Lovastatin (EXCEL) study results: 2-year efficacy and safety follow-up. Am J Cardiol 1994 Oct 1;74(7):667-673.

55. Catapano AL, Reiner Z, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman M, Durrington P, et al. ESC/EAS Guidelines for the management of dyslipidaemias. The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Atherosclerosis 2011 Jul;217(1):3-46.

56. Cohen DE, Anania FA, Chalasani N. An assessment of statin safety by hepatologists. Am J Cardiol 2006 Apr 17;97(8A): 77C-81C.

57. McKenney JM, Davidson MH, Jacobson TA, Guyton JR. Final conclusions and recommendations of the National Lipid Association Statin Safety Assessment Task Force. Am J Cardiol 2006 Apr 17;97(8A):89C-94C.

58. Marcum ZA, Vande Griend JP, Linnebur SA. FDA drug safety communications: a narrative review and clinical considerations for older adults. Am J Geriatr Pharmacother 2012 Aug;10(4):264-271.

59. Vuppalanchi R, Teal E, Chalasani N. Patients with elevated baseline liver enzymes do not have higher frequency of hepatotoxicity from lovastatin than those with normal baseline liver enzymes. Am J Med Sci 2005 Feb;329(2):62-65.

60. Chalasani N, Aljadhey H, Kesterson J, Murray MD, Hall SD. Patients with elevated liver enzymes are not at higher risk for statin hepatotoxicity. Gastroenterology 2004 May;126(5): 1287-1292.

61. Gillett RC, Jr, Norrell A. Considerations for safe use of statins: liver enzyme abnormalities and muscle toxicity. Am Fam Physician 2011 Mar 15;83(6):711-716.

62. Sastre J, Pallardo FV, Vina J. The role of mitochondrial oxidative stress in aging. Free Radic Biol Med 2003 Jul 1;35(1):1-8.

63. Golomb BA, McGraw JJ, Evans MA, Dimsdale JE. Physician response to patient reports of adverse drug effects: implications for patient-targeted adverse effect surveillance. Drug Saf 2007;30(8):669-675.

64. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, Koenig W, Libby P, Lorenzatti AJ, MacFadyen JG, et al. JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008 Nov 20;359(21):2195-2207.

65. Sattar N, Preiss D, Murray H, Welsh P, Buckley B, de Craen A, Seshasai SR, McMurray JJ, Freeman DJ, Jukema JW, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010 Feb 27; 375(9716):735-742.

66. Simsek S, Schalkwijk C, Wolffenbuttel B. Effects of rosuvastatin and atorvastatin on glycemic control in type 2 diabetes: the Corall Study. Diabet Med 2012 May;29(5):628-631.