Problems and Possible Solutions for Therapy with Statins

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Abstract

Despite issues about the value of statins, benefit for high cardiovascular (CV) risk outweighs problems. However, the practitioner must be aware of concerns, be prepared to respond, and justify statin usage. Symptoms of statin-related myopathy are of more concern than stated by pharmaceutical companies. Occurrence of myopathy symptoms, estimated to be up to 10.4%, can decrease statin adherence of high CV risk patients. Dosage modification, or use of pitavastatin, may help the problematic patient. There are concerns that there may be little benefit of statins for primary prevention in women. However, evidence appears to support statin use in women at high CV risk, both in primary and secondary prevention. Abandoning low-density lipoprotein cholesterol (LDL-C) as a valid target is unwarranted; there is much evidence to support "lower is better." The practitioner must be aware of the complicated processes causing atherosclerosis and when to incorporate new approaches to disease management. Tailoring therapy for CV risk, when indicated, may contribute further to LDL-C reduction. Liver inflammation can occur with statins but is of minimal concern; frequently, statins alleviate the problem. Unless liver transaminases are over three times normal, a statin should be prescribed, if indicated. The net effect of statins on cognition appears to be zero—no harm, no benefit. Despite reports of improved cognition, statins should not be prescribed for this. With diabetes mellitus (DM), statins can increase incidence, but the CV benefit far outweighs any risk. Therefore, statins should be prescribed in DM to reduce CV risk. Statins are a major medical contribution when used appropriately.

Keywords
- cognition
- coronary heart disease
- diabetes mellitus
- liver inflammation
- low-density lipoprotein cholesterol
- statin myopathy
- women and heart disease

Statins play a major role in cardiovascular (CV) risk reduction and value is established. There are questions about myopathy,[1,2] women,[3] low-density lipoprotein cholesterol (LDL-C) targets versus a tailored approach,[4,5] liver inflammation,[6] cognition,[7] and increased diabetes mellitus (DM).[8] The objective of this article is to place each one of these problematic questions regarding the clinical use of statins in context, discuss the relevance of each, and present evidence that despite such issues the overall benefit of statins far outweighs any problems. Nevertheless, the clinician must be prepared to deal with concerns that result in decreased adherence to these key CV medications (►**Table 1**).

Specific Concerns Regarding Statins

Myopathy

Statin myopathy symptoms include vague muscle weakness and aches. Pathogenesis is poorly understood.[1] Nevertheless, there are data to suggest that some patients are susceptible to statin myopathy because of preexisting subclinical inherited muscular disorders or a genetic variation in statin uptake proteins encoded by SLCP1B1 or the cytochrome P enzyme system.[9] Myopathy may be insignificant or significant; fortunately, a serious rhabdomyolysis is infrequent. Significant myopathy is defined as creatine kinase (CK) activity greater than 10 times the upper limit of normal.[2] Statin myopathy

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Table 1 Statins: potential problems and concerns

Possible concerns with statins	Status
Myopathy	A significant problem for many patients that must be dealt with
Women: benefit versus harm	Some differences in women but no question of overall CV benefit
Decreased CV benefit	Some concerns raised by statistical manipulations but overall CV benefit clear
LDL-C targets	An established valuable approach subject to added benefit when additional tailored approach is backed by evidence
Liver inflammation	A minimal problem frequently lessened by a statin
Cognition	The overall analysis is no significant harm or improvement
Diabetes mellitus	Evidence for increased clinical presentation induced by statins but CV benefit far outweighs problem

Abbreviations: CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol.

symptoms can also occur with a normal CK.[10] Many brief, randomized, controlled, clinical trials (RCCTs) have reported no increased myopathy, even with markedly elevated statin dose.[11–13] A meta-analysis of seven RCCTs involving 29,395 patients reported no significant increased myopathy with intensive statin therapy. However, in this meta-analysis, evidence of myopathy was noted in some component trials and also a 0.5% increased incidence of myopathy with more intensive therapy.[14] The large French observational study, Prediction of Muscular Risk in Observational Conditions of 7,924 patients on high-dose statins, reported 10.5% of the patients had muscle-related symptoms at a median of 1 month.[15]

Myopathy from statins is not as trivial as that reported. Many RCCTs have a run-in, in which participants with problems with the trial medication are eliminated.[16] With much evidence for decreasing LDL-C as the gold standard for CV risk reduction (despite other factors), much can be said for lower statin doses to attain similar LDL-C reduction, such as by addition of ezetimibe.[1] Exception to avoiding a high-dose statin involves studies with benefit from atorvastatin 80 mg/day at onset of acute coronary syndrome.[12] Once the acute phase is over (e.g., 3 months), it appears appropriate to lower the dose, while maximizing LDL-C reduction. Ezetimibe can contribute up to 26% additional reduction in LDL-C while maintaining a safer lower statin dose.[17] Also ezetimibe may contribute to diminished CV risk by decreasing inflammation, as evidenced by its reduction in high-sensitivity C-reactive protein (hsCRP).[18]

Myopathy symptoms are significant in many patients and interfere with statin adherence. Coenzyme Q may alleviate these symptoms although unconfirmed by RCCTs. Scientific basis for its use is its decreased biosynthesis by statins.[19] Rosuvastatin in a decreased dose twice a week has been shown to have benefit.[20] Pitavastatin decreases coenzyme Q less than other statins and may have improved tolerance in comparison.[21] In addition, there is evidence of a vitamin D receptor present in skeletal muscle and that vitamin D deficiency can cause myopathy. However, as reviewed by Gupta and Thompson, additional study is essential to define the role of vitamin D in statin myopathy before a specific supplementation recommendation when muscle complaints are present, although this could be tried in the presence of clinical vitamin D deficiency.[22]

Women: No Benefit of Statin or Even Harm?

Women have been considered problematic for aggressive management of CV disease due to physiologic differences and differences in CV risk reduction, especially questions of benefit from primary prevention. A long-standing critique of trials is failure to include women. Also, there has been criticism of failure to render CV care to women comparable with men. CV symptoms in women do not receive the same attention. However, the focus of this article is use of statins and associated problems. There is a concern that there may be little primary prevention benefit of statins and/or lipid lowering in women. In a 2004 meta-analysis of lipid lowering studies, Walsh and Pignone analyzed six trials with a total of 11,435 women without evident CV disease; they found that lipid-lowering medications did not significantly reduce total mortality, coronary heart disease (CHD) mortality, nonfatal myocardial infarction (MI), revascularization, or CHD events.[3] Such results question whether primary prevention of CV disease in women is beneficial. Although eight trials including 8,272 women with CV disease showed that lipid lowering did *not* decrease total mortality, it did reduce their CHD mortality, nonfatal MIs, and total CHD events—consistent with benefit for women with CV disease.[3] However, in a small meta-analysis of five trials involving statins, LaRosa et al[23] in 1999 reported that an observed moderate lipid lowering with statins had essentially equal benefit in women and men. There was an average LDL-C reduction of 28% with an associated decrease in major coronary events of 31% in men and 29% in women. These results were essentially the same for both sexes and the slight difference was not statistically significant.[23]

Induction of DM in women by statins is an issue (as in men) and this will be discussed further in the subsequent section. In the Women's Health Initiative (WHI) study, Culver et al highlighted this problem in 153,840 women without DM, 7.04% of who were taking a statin at baseline.[24] Subsequently,

there were 10,242 incident cases of self-reported DM during 1,004,466 person-years of follow-up. In this study of postmenopausal women, the authors found that a statin at baseline resulted in an adjusted 48% increased risk of DM (multivariate adjusted hazard ratio [aHR], 1.48; 95% CI, 1.38 to 1.59). This was further confirmed by subset analyses of an association of DM with longitudinal measures of statin use in 125,575 women.

More recent meta-analyses have not resolved the issue of statin treatment in women. Kostis et al[25] reported in 2012 on their analysis of 18 RCCTs of statins with sex-specific outcomes ($N = 141,235$; this encompassed a total of 21,468 CV events). There were 40,275 women included in their meta-analysis. The CV-event rate was lower with randomization to statin intervention as compared with the control.[25] Benefit from statins was significant in both sexes, regardless of type of control, baseline risk, or endpoint, and this applied to both primary and secondary prevention. Also, all-cause mortality was lower with statin therapy both in women and in men with no sex difference. The authors emphasized statin use in patients without consideration of sex. However, in a very recent meta-analysis involving 11 RCCTs with 43,193 patients, Gutierrez et al noted a sex difference for secondary prevention of CV events.[26] Statin therapy was effective for secondary prevention of CV events in both sexes, but there was no benefit for stroke or all-cause mortality in women. The clinician needs to be aware of the issues discussed regarding possible sex differences, but continued use of statins in women where indicated by increased CV risk appears appropriate.

Decreased or No Benefit from Statins

Benefit of statins for reducing CV risk appears well accepted due to classic outcomes studies.[27–30] Nevertheless, it is essential to present the other side when questions have been raised. Thus, it is appropriate to discuss a meta-analysis of 11 RCCTs involving 65,229 patients, as reported by Ray et al.[31] Actually, two of the classic statin outcomes studies, the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS)[30] and the West of Scotland Coronary Prevention Study Group (WOSCOPS),[29] were included. Ray et al specifically stated that all systematic reviews before their meta-analysis included trials that partially incorporated patients with known CV disease.[31] Their objective was to discern whether statins given to intermediate- to high-risk individuals with no history of CV disease resulted in reduction of all-cause mortality. They combined data from 11 studies using a random-effects model with meta-analysis and assessed heterogeneity with a so-called I^2 statistic.[32] In synthesizing analyzed data, they stated that data were available from 65,229 participants followed for approximately 244,000 person-years.[31] During this, there were 2,793 deaths. Use of statins in high-risk primary prevention situations analyzed was not associated with significant CV risk reduction (HR, 0.91; 95% CI, 0.83 to 1.01). They found no significant evidence for heterogeneity among the studies ($I^2 = 23\%$; 95% CI, 0 to 61% [$p = 0.23$]). They concluded that there was *no* evidence for benefit of statins for primary prevention of all-cause mortality in patients with high CV risk. In commenting on Ray et al, Redberg noted the need for pause in the common practice of prescribing statins for primary CV disease prevention, especially in lower risk patients.[33] This is certainly not the generally accepted interpretation of the classic outcomes studies with statins, but must be considered by experts in the field. Future impartial studies may explain such observations. WOSCOPS was a primary prevention study in patients with no prior history of MI.[29] In the same issue of *Arch Intern Med* (Ray et al[31]), and in a scathing critique of the Justification for the Use of Statins in Primary Prevention (JUPITER) trial,[34] de Lorgeril et al[35] concluded that JUPITER was flawed, with major discrepancy between significant reduction in nonfatal stroke and MI (no effect on mortality from stroke and MI), a surprisingly low CV mortality compared with total mortality, and a very low case-fatality rate of MI below expected. They commented on possible bias having entered the trial due to strong commercial association. On initial assessment, JUPITER was another outcomes study supporting LDL-C reduction as well as significance of hsCRP, but with definite concerns regarding marketing of rosuvastatin.[36] Therefore, de Lorgeril et al[35] concluded that JUPITER did not support use of statins for primary prevention of CV disease and raised troubling questions concerning the role of commercial sponsors. Also, in the same issue of *Arch Intern Med*, Green editorialized that the meta-analysis by Ray et al showed that any benefit for true primary prevention was at best very small and that long-term benefit was still not established.[37] Green furthermore editorialized that, as pointed out by de Lorgeril et al, "research must be free of incentives to find any particular desired answer."

Such analyses of statin trials as noted above are not accepted by those believing in the lipid hypothesis and in CV risk reduction by decreasing LDL-C. However, attention must be paid to opposing opinions/interpretations of the best in evidence-based medicine. In a contrasting meta-analysis, Brugts et al[38] studied the benefit of statin in 10 trials with a total of 70,388 individuals with CV risk factors but no established CV disease. Included were 23,681 women and 16,078 diabetic patients. Interestingly, two of the ten trials used by Ray et al[31] were also part (WOSCOPS[29] and AFCAPS/TexCAPS[30]) of the meta-analysis of Brugts et al.[38] It was concluded that without established CV disease but with CV risk factors, statins resulted in significantly improved survival and large reductions in risk of major CV events.[38] Each clinician must make his or her own decision on statins for CV risk reduction, based on interpretation of available evidence.

Low-Density Lipoprotein Cholesterol: Targeted versus Tailored

To some clinicians/researchers, lowering LDL-C is the "gold standard" of CV risk management. Gold standard may be too strong for others, but there is definitely extensive evidence for LDL-C reduction as a target for decreasing CV risk. This association has been well established by studies of different focus before the statin era and with essentially pure LDL

reduction, free of major additional pharmacologic effects. These studies include the Lipid Research Clinics study using cholestyramine,[39,40] quantitative coronary angiography with atherosclerosis plaque regression in the Cholesterol Lowering Atherosclerosis Study (CLAS) using colestipol plus nicotinic acid,[41,42] ileal bypass in the Program on the Surgical Control of the Hyperlipidemias (POSCH),[43,44] LDL-C apheresis,[45] and hypobetalipoproteinemia (associated with a very low incidence of CV disease).[46] Additional studies involving statins that confirm lower LDL-C include the Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 (PROVE-IT-TIMI 22) study in acute coronary syndrome patients,[47] the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study of secondary CHD prevention,[48] the JUPITER substudy attaining LDL-C $<$ 50 mg/dL,[49] and the 2004 assessment of trials for the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines with straight-line decrease in relative CHD risk down to LDL-C 40 mg/dL.[50]

Evidence noted above and key statin outcomes studies already cited are the basis for a targeted approach to LDL-C. Any knowledgeable clinician/investigator knows that atherosclerosis has other complex issues and that inflammation, the pleiotropic effects of the statins, high-density lipoprotein cholesterol (HDL-C), and other undefined factors play a role in CV risk. Although many practicing clinicians on the front lines of medicine are finally accepting the importance of LDL-C reduction and prescribing statins, it is not at all uncommon to see cardiologists not prescribing statin or other medications to high CV risk patients.[5] To complicate this, Hayward and Krumholz have advocated the abandonment of LDL-C targets, to be replaced by their "tailored" approach.[4] Abandoning LDL-C as a target appears premature and may confuse many clinicians just beginning to treat CV risk. Of course, new approaches deserve evaluation and consideration of their place in the entire CV continuum.

Liver Inflammation

Prescribing a statin with elevated liver enzymes is an important issue for clinicians, and available data are critical for how to proceed. Elevated liver transaminases occur in up to 2.0% of patients on a statin and appear to be dose dependent.[6] However, transaminase elevation may not be true hepatotoxicity and elevations considered significant (more than three times upper limit of normal) in large trials have been essentially the same for the statin versus placebo. Contributing to the confusion, patients with high CV risk with comorbid conditions, such as metabolic syndrome, DM, and obesity, can have associated inflammatory conditions of the liver, inseparable from statin-induced inflammation.[51] In a post hoc analysis of GREACE, Athyros et al studied 437 patients at baseline with moderately abnormal liver function tests (LFTs) possibly associated with nonalcoholic fatty liver disease (NAFLD).[52] Of these, 227 on an average dose of atorvastatin 24 mg/day showed significant improvement in their LFTs. The remaining 210 not treated with a statin had further increases in their LFTs ($p < 0.001$). CV events occurred in 22 (10%) of the 227 patients with abnormal LFTs and in 63 (30%) of the 210 patients with abnormal LFTs not receiving a statin. Also, CV disease benefit was greater ($p = 0.0074$) in patients on a statin with abnormal LFTs than in patients (653) with normal LFTs. Of their patients receiving a statin, $<$ 1% discontinued it due to transaminase levels more than three times upper normal. The results of Athyros et al were consistent with safety of statins for the liver. Also, statins may improve LFTs in patients with NAFLD while reducing CV morbidity.[52]

Han et al reported on short-term safety and efficacy of statins in 189 patients with elevated LDL-C and elevated serum alanine transaminase (ALT) in the PITCH study (PITavastatin versus atorvastatin to evaluate the effect on patients with hypercholesterolemia and mild to moderate hepatic damage).[53] The 135 patients with elevated ALT levels at randomization had significant reductions in ALT after 12 weeks of pitavastatin or atorvastatin. A total of 38 patients with hepatic steatosis, followed with serial non-enhanced computed tomography, were shown to have decreased steatosis with both statins. Wierzbick and Oben, in a 2012 article, reviewed the mechanisms leading to NAFLD and nonalcoholic steatosis and concluded that there is trial evidence to support some improvement in steatosis in association with statins.[54] There is even data that statins may offer some protection to decrease hepatic injury following anthracyclines used in cancer treatment.[55]

Unfortunately, concerns of hepatotoxicity have contributed to underutilization of statins in primary care.[56] Fortunately, there is rarely a significant problem of liver inflammation associated with statins, and frequently, statins result in a decrease in abnormal LFTs. There may be even greater CV benefit for statin use in patients with some abnormal liver function.

Alteration of Cognition

Any effect of statin on cognition has been a significant concern. Alzheimer disease (AD) is the most common problem that results in cognitive decline at advanced age and is premature in some individuals. The neuropathology appears progressive and irreversible. Cholesterol represents an important determinant of status of biological membranes.[57] In brain specimens from patients with AD, there are specific changes in membrane ordering and a loss in membrane cholesterol content. This appears to make statins possibly problematic, especially if lipophilic. There are even reports that switching from lipophilic to hydrophilic statins may resolve any associated cognitive impairment.[58] Nevertheless, some clinical studies suggest decreased AD in patients taking statins but nonrandomization of these trials makes them inconclusive.[57]

Researching the literature leads to reports of favorable effects of statins on AD and reports of negative effects. The best approach is to find larger studies and then try to make conclusions. Li et al studied members of a health maintenance organization (HMO) who were $\geq$ 65 years of age without detectable dementia.[59] Over 6.1 years of follow-up of 3,099 participants, 263 developed probable AD. For age $<$ 80 years,

the aHR for strength of association of AD with a statin was 0.44 (95% CI = 1.25 to 0.78, $p = 0.04$). For $\geq$ 80 years, the aHR was 1.22 (95% CI = 0.61 to 2.42, $p = 0.65$). Interpretation was that statin use in early old age may be associated with lower risk of AD but not in later old age.[59] However, in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) study, Trompet et al studied 5,804 participants at six different times using four neuropsychological performance tests for a mean follow-up of 42 months.[60] They concluded that there was no difference in cognitive decline in participants treated with pravastatin compared with placebo and therefore no reason to prescribe statin therapy in the elderly to benefit cognition. Glasser et al, in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, made a cross-sectional analysis of 7,191 statin users and 17,404 nonusers, age $\geq$ 45 years in a population-based national cohort study.[61] Oversampling occurred from the southeastern Stroke Belt and African Americans. They assessed cognitive performance with a previously validated instrument of global cognitive status. They initially concluded that statins were marginally associated with cognitive impairment, but after adjusting for known variables, they determined there was no association. Also, there were no regional differences. This large study suggested that there is no evidence for an association between cognition and statins.[61] In a Cochrane Database analysis, McGuinness et al found insufficient evidence to recommend statins for dementia.[7]

The reality is that a possible benefit of statin for AD has not been eliminated. In a brief review, Sabbagh and Sparks[62] are of the opinion that much epidemiological data support risk reduction for AD with statins. On the contrary, the authors comment on "lingering" disparities with clinical trials, which offer little support for statin benefit to decrease AD. They consider now is the time to bridge pools of clinical data by pursuing a statin primary prevention trial. Obviously, the issue is not resolved, but a prudent approach to statin use appears to be their use in the elderly as recommended for CV risk reduction and not specifically for any cognitive benefit.

Increase in Diabetes Mellitus?

Any role of statins in increasing DM has created much concern. Assesment of available data and its interpretation should help the clinician be comfortable with using statins for CV risk reduction after considering established major benefit versus minimal risk from increased DM. Sattar et al performed a meta-analysis of 13 trials with 91,140 participants.[8] They concluded statins were associated with a decrease in major coronary events (CHD death and nonfatal MI): 5.4 events per 255 patients treated for 4 years, compared with controls and associated with a 1 mmol/L (38.66976 mg/dL) decrease in LDL-C. The same 255 patients resulted in one additional case of DM. The authors stated that the obvious benefit in favor of the statin would be even greater if the decrease in strokes and revascularizations were taken into account.[8] Culver et al assessed data from postmenopausal women in the WHI[24]; the data included 153,840 women without DM and included 7.04% who reported taking a statin medication. Over 1,004,466 person-years of follow-up, there were 10,242 incident cases of self-reported DM. Statin use at baseline was associated with increased risk of DM (HR, 1.71; 95% CI, 1.61 to 1.83), still present after adjusting for other potential cofounders (HR, 1.48; 95% CI, 1.38 to 1.59). It was concluded that statins in postmenopausal women have an association with increased DM.

On the other hand, studies have suggested benefit of statins for DM itself. In WOSCOPS, Freeman et al concluded that pravastatin resulted in a 30% reduction ($p = 0.042$) in development of DM.[63] It was considered that by lowering plasma triglycerides, pravastatin may favorably influence appearance of DM plus its anti-inflammatory, and endothelial effects may be beneficial. Dalla Nora et al studied 25 type 2 DM patients free of microangiopathic complications and with LDL-C $<$ 180 mg/dL.[64] Patients were randomized to receive atorvastatin or placebo for 12 months. The atorvastatin group showed not only reduced LDL-C but also improved glycemic control. Huptas et al studied the effect of 6 weeks of atorvastatin, 10 mg/day, in 10 insulin-resistant subjects and found significant improvement in insulin sensitivity, measured by the homeostasis model assessment index.[65]

The JUPITER trial analyzed two groups of patients with DM to assess any relationship to rosuvastatin. In Group 1 with no major DM risk factors ($n = 6{,}095$), statin use was associated with a 52% decrease in the primary endpoint (MI, stroke, unstable angina admission, arterial revascularization, or CV death), 22% decrease in total mortality, and no increase in DM.[66] This resulted in avoidance of 86 vascular events or deaths and no new cases of DM. In Group 2, rosuvastatin use in participants with one or more major DM risk factors ($n = 11{,}508$) was associated with 39% decrease in the primary endpoint, 17% decrease in total mortality, and 28% increase in DM. Nevertheless, 134 vascular events or deaths were avoided in exchange for 54 new cases of DM.[66]

Information, analysis, and reviews continue to appear in the literature regarding an association of statins with DM. Colbert and Stone reviewed the issues and recognized the concerns that had been raised regarding an increased incidence of new-onset DM.[67] They commented that most randomized, placebo-controlled trials involving statins have not included the incidence of new-onset DM as a major primary endpoint. However, they recognized that a very small but consistent adverse effect on glycosylated hemoglobin and blood glucose levels had been observed. And, they considered the clinical significance of this still unknown and noted that patient subgroups placed on a statin such as those with the metabolic syndrome may be especially susceptible to developing DM. Jukema et al weighed the evidence of the controversies in statin therapy and commented on the small increase in risk of type 2 DM, but they considered this small risk is outweighed by the CV benefit of statins in patients where such therapy is recommended.[68] Were concerns to increase regarding statins and DM, a 2013 meta-analysis by Navarese et al may have value for the clinician, since they found that different types and doses of statins vary in their potential to increase the incidence of DM.[69] They found that pravastatin in a dose of 40 mg/day had

the lowest incidence, atorvastatin 80 mg/day was intermediate, and rosuvastatin 20 mg/day was highest. Shah and Goldfine suggest monitoring blood sugar control in patients at risk for DM when a statin has been prescribed, and a statin should be continued only when indicated for the prevention of increased CV disease risk.[70] In a review by Rocco, it was noted that statins now have a US Food and Drug Administration warning that they may increase the risk of DM and may worsen blood sugar control in preexisting DM is recognized. However, his review concluded that there is no evidence that an increased blood sugar while taking a lipid-lowering medication is associated with increased risk for CV events or that there is an attenuation of the beneficial effect of such therapy.[71] It appears that as of this moment, the benefit of CV risk reduction by statins far outweighs any risk of associated development or exacerbation of DM.

Conclusion

Despite some concerns, benefit from statins in high CV risk far outweighs any problems. Nevertheless, the clinician must be aware of concerns that patients and other health practitioners may have and be prepared to respond and justify use of these key CV medications. Statin-related myopathy, especially symptoms, is of more concern than stated by pharmaceutical companies. There are differences involving women and statins but no valid question of their CV benefit. Abandoning LDL-C as a target appears unwarranted; there is much evidence to support "lower is better." Nevertheless, health practitioners must be aware of the complicated processes causing atherosclerosis and when to incorporate new approaches. Liver inflammation can occur with statins but is a minimal problem; in many cases, statins alleviate the problem. The sum effect of statins on cognition appears to, in general, be zero—no harm, no benefit. Statins increase the occurrence of DM but the CV benefit far outweighs any risk for DM. Statins are one of our major medical advances when used appropriately.

References

1 Whayne TF Jr. Statin myopathy: significant problem with minimal awareness by clinicians and no emphasis by clinical investigators. Angiology 2011;62(5):415–421
2 Silva MA, Swanson AC, Gandhi PJ, Tataronis GR. Statin-related adverse events: a meta-analysis. Clin Ther 2006;28(1):26–35
3 Walsh JM, Pignone M. Drug treatment of hyperlipidemia in women. JAMA 2004;291(18):2243–2252
4 Hayward RA, Krumholz HM. Three reasons to abandon low-density lipoprotein targets: an open letter to the Adult Treatment Panel IV of the National Institutes of Health. Circ Cardiovasc Qual Outcomes 2012;5(1):2–5
5 Whayne TF Jr. Assessment of low-density lipoprotein targets. Angiology 2012 Jun 25. [Epub ahead of print], PMID: 22734087 [PubMed- as supplied by publisher].
6 National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). 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) final report. Circulation 2002;106 (25):3143–3421
7 McGuinness B, O'Hare J, Craig D, Bullock R, Malouf R, Passmore P. Statins for the treatment of dementia. Cochrane Database Syst Rev 2010; (8):CD007514
8 Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010;375(9716):735–742
9 Ghatak A, Faheem O, Thompson PD. The genetics of statin-induced myopathy. Atherosclerosis 2010;210(2):337–343
10 Phillips PS, Haas RH, Bannykh S, et al; Scripps Mercy Clinical Research Center. Statin-associated myopathy with normal creatine kinase levels. Ann Intern Med 2002;137(7):581–585
11 Nissen SE, Tuzcu EM, Schoenhagen P, et al; REVERSAL Investigators. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: a randomized controlled trial. JAMA 2004;291(9):1071–1080
12 Cannon CP, Braunwald E, McCabe CH, et al; Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 Investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. N Engl J Med 2004;350(15):1495–1504
13 Nissen SE, Nicholls SJ, Sipahi I, et al; ASTEROID Investigators. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: the ASTEROID trial. JAMA 2006;295(13):1556–1565
14 Josan K, Majumdar SR, McAlister FA. The efficacy and safety of intensive statin therapy: a meta-analysis of randomized trials. CMAJ 2008;178(5):576–584
15 Bruckert E, Hayem G, Dejager S, Yau C, Bégaud B. Mild to moderate muscular symptoms with high-dosage statin therapy in hyperlipidemic patients—the PRIMO study. Cardiovasc Drugs Ther 2005;19(6):403–414
16 Pablos-Méndez A, Barr RG, Shea S. Run-in periods in randomized trials: implications for the application of results in clinical practice. JAMA 1998;279(3):222–225
17 Gazi IF, Daskalopoulou SS, Nair DR, Mikhailidis DP. Effect of ezetimibe in patients who cannot tolerate statins or cannot get to the low density lipoprotein cholesterol target despite taking a statin. Curr Med Res Opin 2007;23(9):2183–2192
18 Sager PT, Melani L, Lipka L, et al; Ezetimibe Study Group. Effect of coadministration of ezetimibe and simvastatin on high-sensitivity C-reactive protein. Am J Cardiol 2003;92(12):1414–1418
19 Crane FL. Biochemical functions of coenzyme Q10. J Am Coll Nutr 2001;20(6):591–598
20 Gadarla M, Kearns AK, Thompson PD. Efficacy of rosuvastatin (5. mg and 10 mg) twice a week in patients intolerant to daily statins. Am J Cardiol 2008;101(12):1747–1748
21 Kawashiri MA, Nohara A, Tada H, et al. Comparison of effects of pitavastatin and atorvastatin on plasma coenzyme Q10 in heterozygous familial hypercholesterolemia: results from a crossover study. Clin Pharmacol Ther 2008;83(5):731–739
22 Gupta A, Thompson PD. The relationship of vitamin D deficiency to statin myopathy. Atherosclerosis 2011;215(1):23–29
23 LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. JAMA 1999;282(24):2340–2346
24 Culver AL, Ockene IS, Balasubramanian R, et al. Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative. Arch Intern Med 2012;172(2): 144–152
25 Kostis WJ, Cheng JQ, Dobrzynski JM, Cabrera J, Kostis JB. Meta-analysis of statin effects in women versus men. J Am Coll Cardiol 2012;59(6):572–582
26 Gutierrez J, Ramirez G, Rundek T, Sacco RL. Statin therapy in the prevention of recurrent cardiovascular events: a sex-based meta-analysis. Arch Intern Med 2012;172(12):909–919
27 Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344(8934):1383–1389

28 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(19):1349–1357

29 Shepherd J, Cobbe SM, Ford I, et al; West of Scotland Coronary Prevention Study Group. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. N Engl J Med 1995;333(20):1301–1307

30 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(20): 1615–1622

31 Ray KK, Seshasai SR, Erqou S, et al. Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65,229 participants. Arch Intern Med 2010;170(12):1024–1031

32 Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557–560

33 Redberg RF. Update in cardiology: evidence published in 2010. Ann Intern Med 2011;154(8):549–553

34 Ridker PM, Danielson E, Fonseca FA, et al; JUPITER Study Group. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 2008;359(21):2195–2207

35 de Lorgeril M, Salen P, Abramson J, et al. Cholesterol lowering, cardiovascular diseases, and the rosuvastatin-JUPITER controversy: a critical reappraisal. Arch Intern Med 2010;170(12):1032–1036

36 Whayne TF Jr. Astronomical science or astronomical marketing? Clin Geriatrics 2009;17:36

37 Green LA. Cholesterol-lowering therapy for primary prevention: still much we don't know. Arch Intern Med 2010;170(12):1007–1008

38 Brugts JJ, Yetgin T, Hoeks SE, et al. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. BMJ 2009;338:b2376

39 The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. JAMA 1984;251(3):351–364

40 The Lipid Research Clinics Coronary Primary Prevention Trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. JAMA 1984;251(3):365–374

41 Blankenhorn DH, Johnson RL, Nessim SA, Azen SP, Sanmarco ME, Selzer RH. The Cholesterol Lowering Atherosclerosis Study (CLAS): design, methods, and baseline results. Control Clin Trials 1987;8(4): 356–387

42 Blankenhorn DH, Nessim SA, Johnson RL, Sanmarco ME, Azen SP, Cashin-Hemphill L. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. JAMA 1987;257(23):3233–3240

43 Buchwald H, Stoller DK, Campos CT, Matts JP, Varco RL. Partial ileal bypass for hypercholesterolemia. 20- to 26-year follow-up of the first 57 consecutive cases. Ann Surg 1990;212(3):318–329, discussion 329–331

44 Buchwald H, Varco RL, Boen JR, et al. Effective lipid modification by partial ileal bypass reduced long-term coronary heart disease mortality and morbidity: five-year posttrial follow-up report from the POSCH. Program on the Surgical Control of the Hyperlipidemias. Arch Intern Med 1998;158(11):1253–1261

45 Moriarty PM. LDL-apheresis therapy. Curr Treat Options Cardiovasc Med 2006;8(4):282–288

46 Schonfeld G. The hypobetalipoproteinemias. Annu Rev Nutr 1995;15:23–34

47 Wiviott SD, Cannon CP, Morrow DA, Ray KK, Pfeffer MA, Braunwald E; PROVE IT-TIMI 22 Investigators. Can low-density lipoprotein be too low? The safety and efficacy of achieving very low low-density lipoprotein with intensive statin therapy: a PROVE IT-TIMI 22 substudy. J Am Coll Cardiol 2005;46(8):1411–1416

48 Athyros VG, Papageorgiou AA, Mercouris BR, et al. Treatment with atorvastatin to the National Cholesterol Educational Program goal versus 'usual' care in secondary coronary heart disease prevention. The GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. Curr Med Res Opin 2002;18(4): 220–228

49 Hsia J, MacFadyen JG, Monyak J, Ridker PM. Cardiovascular event reduction and adverse events among subjects attaining low-density lipoprotein cholesterol <50 mg/dl with rosuvastatin. The JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin). J Am Coll Cardiol 2011;57(16):1666–1675

50 Grundy SM, Cleeman JI, Merz CN, et al; National Heart, Lung, and Blood Institute; American College of Cardiology Foundation; American Heart Association. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. Circulation 2004;110(2):227–239

51 Pascale A, Pais R, Ratziu V. An overview of nonalcoholic steatohepatitis: past, present and future directions. J Gastrointestin Liver Dis 2010;19(4):415–423

52 Athyros VG, Tziomalos K, Gossios TD, et al; GREACE Study Collaborative Group. Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: a post-hoc analysis. Lancet 2010;376(9756):1916–1922

53 Han KH, Rha SW, Kang HJ, et al. Evaluation of short-term safety and efficacy of HMG-CoA reductase inhibitors in hypercholesterolemic patients with elevated serum alanine transaminase concentrations: PITCH study (PITavastatin versus atorvastatin to evaluate the effect on patients with hypercholesterolemia and mild to moderate hepatic damage). J Clin Lipidol 2012;6(4): 340–351

54 Wierzbicki AS, Oben J. Nonalcoholic fatty liver disease and lipids. Curr Opin Lipidol 2012;23(4):345–352

55 Henninger C, Huelsenbeck J, Huelsenbeck S, et al. The lipid lowering drug lovastatin protects against doxorubicin-induced hepatotoxicity. Toxicol Appl Pharmacol 2012;261(1):66–73

56 Rzouq FS, Volk ML, Hatoum HH, Talluri SK, Mummadi RR, Sood GK. Hepatotoxicity fears contribute to underutilization of statin medications by primary care physicians. Am J Med Sci 2010;340 (2):89–93

57 Biondi E. Prescription of lipophilic statins to Alzheimer's disease patients: some controversies to consider. Neurol Sci 2011;32 (2):195–201

58 Rojas-Fernandez CH, Cameron JC. Is statin-associated cognitive impairment clinically relevant? A narrative review and clinical recommendations. Ann Pharmacother 2012;46(4):549–557

59 Li G, Shofer JB, Rhew IC, et al. Age-varying association between statin use and incident Alzheimer's disease. J Am Geriatr Soc 2010;58(7):1311–1317

60 Trompet S, van Vliet P, de Craen AJ, et al. Pravastatin and cognitive function in the elderly. Results of the PROSPER study. J Neurol 2010;257(1):85–90

61 Glasser SP, Wadley V, Judd S, et al. The association of statin use and statin type and cognitive performance: analysis of the reasons for geographic and racial differences in stroke (REGARDS) study. Clin Cardiol 2010;33(5):280–288

62 Sabbagh MN, Sparks DL. Statins to treat Alzheimer's disease: an incomplete story. Expert Rev Neurother 2012;12(1):27–30

63 Freeman DJ, Norrie J, Sattar N, et al. Pravastatin and the development of diabetes mellitus: evidence for a protective treatment effect in the West of Scotland Coronary Prevention Study. Circulation 2001;103(3):357–362

64 Dalla Nora E, Passaro A, Zamboni PF, Calzoni F, Fellin R, Solini A. Atorvastatin improves metabolic control and endothelial function in type 2 diabetic patients: a placebo-controlled study. J Endocrinol Invest 2003;26(1):73–78

65 Huptas S, Geiss HC, Otto C, Parhofer KG. Effect of atorvastatin (10 mg/day) on glucose metabolism in patients with the metabolic syndrome. Am J Cardiol 2006;98(1):66–69
66 Ridker PM, Pradhan A, MacFadyen JG, Libby P, Glynn RJ. Cardiovascular benefits and diabetes risks of statin therapy in primary prevention: an analysis from the JUPITER trial. Lancet 2012;380(9841):565–571
67 Colbert JD, Stone JA. Statin use and the risk of incident diabetes mellitus: a review of the literature. Can J Cardiol 2012;28(5):581–589
68 Jukema JW, Cannon CP, de Craen AJ, Westendorp RG, Trompet S. The controversies of statin therapy: weighing the evidence. J Am Coll Cardiol 2012;60(10):875–881
69 Navarese EP, Buffon A, Andreotti F, et al. Meta-analysis of impact of different types and doses of statins on new-onset diabetes mellitus. Am J Cardiol 2013 Jan 24 [Epub ahead of print]. PMID: 23352266 [PubMed-as supplied by publisher].
70 Shah RV, Goldfine AB. Statins and risk of new-onset diabetes mellitus. Circulation 2012;126(18):e282–e284
71 Rocco MB. Statins and diabetes risk: fact, fiction, and clinical implications. Cleve Clin J Med 2012;79(12):883–893