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Does Upsizing Statins have a Downside?

Chatzizisis et al.[1] offer a timely review of HMG-CoA reductase inhibitor ('statin')-induced myopathy. Although there are new therapies on the horizon that may one day replace the statin class of drugs,[2] the statins are not going anywhere anytime soon. These highly successful drugs will doubtless remain the cornerstone of treating cardiovascular disease for some years to come. In light of this and in view of the safety concerns mentioned by Chatzizisis and colleagues,[1] it is important to appreciate that prescription patterns of statins have shifted dramatically over the past decade.

Statins are the most-commonly prescribed class of drugs in industrialized countries. For example, in Australia, which has comprehensive and readily accessible prescription data, the absolute volume and cost of statin prescriptions have increased 4- and 5-fold, respectively, over the last 12 years (table I). In fact, the percentage of total drug costs attributed to statins has doubled since 1998. There is a strong likelihood that statin usage will continue to climb, given that a substantial proportion of patients at high risk of cardiovascular disease are currently not prescribed statins.[4] Furthermore, statin therapy is expanding beyond the traditional cardiovascular area, with statins currently being tested for a remarkable diversity of diseases, including Alzheimer's disease, asthma, lupus, sepsis, renal diseases and various cancers.

Although statins are considered comparatively safe, like any other drugs they are not free of adverse effects. Often these manifest in combination with other drugs. Most documented adverse reactions are raised liver enzymes and the muscle-related symptoms that were the focus of the review by Chatzizisis and colleagues.[1] These include myalgia, myositis and, rarely, rhabdomyolysis. Other reported adverse effects are not always recognized by health professionals, and include cognitive and memory loss, perturbed glucose metabolism, sexual dysfunction and mood disorders.[5] Whilst hard data on the frequency of statin adverse effects is elusive, estimates of the rate of myalgia in statin-treated patients range from 0.1% to 20%.[2,6] Even if an adverse effect is rare, it becomes a potential public health issue if the drugs are as commonly prescribed as the statins. Moreover,

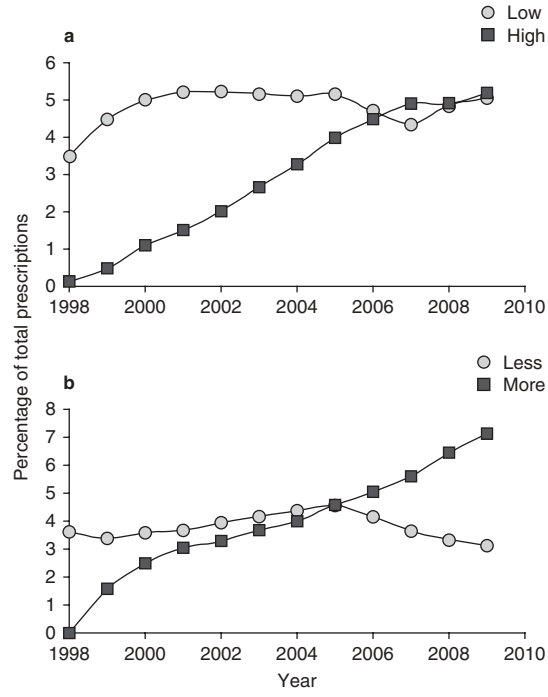

Fig. 1. HMG-CoA reductase inhibitor ('statin') prescription patterns in Australia, 1998–2009. (**a**) For dosage, 'low' is 10 or 20 mg/day; 'high' is 40 or 80 mg/day. (**b**) For potency, 'less' includes pravastatin and simvastatin; 'more' comprises atorvastatin and rosuvastatin. Whilst low dose/less potent statin prescriptions have changed little, high dose/more potent statin prescriptions have risen greatly over the past 12 years (calculated from the Pharmaceutical Benefits Pricing Authority annual reports[3]).

Table I. Statin prescriptions and cost in Australia (calculated from the Pharmaceutical Benefits Pricing Authority annual reports[3])

Volume of prescriptions and cost	1998	2009	Fold-increase
Millions of prescriptions	4.5	18.6	4.1
Total prescriptions (%)	3.6	10.3	2.8
Billions of dollars ($A)[a]	0.2	1.2	5.0
Total cost (%)	7.8	15.4	2.0

a Figures are year 1998 and 2009 values, respectively.

adverse effects tend to increase with the potency and dose of statin used.[5] Importantly, both have risen markedly in Australia, and presumably elsewhere in the world, over the past decade (figure 1). With statin use, dose and potency all on the rise, the number of adverse reactions can be expected to also increase, and health professionals are urged to be vigilant. If a patient is suspected of having an adverse reaction to a statin, a lower dose or less potent version should be considered, or an alternative lipid-lowering therapy tried. Any suspected adverse reaction to a medicine should be reported to the appropriate agency.

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The Authors' Reply

We read with great interest the letter by Dr Brown about our review article regarding risk factors of HMG-CoA reductase inhibitor ('statin')-induced myopathy.[1] We appreciate Dr Brown's cautious approach and reinforce his concerns in our review.

A vast body of evidence has established the beneficial effect of statins in reducing cardiovascular events, and improving cardiovascular and all-cause mortality. Dr Brown correctly underscores the increasing trend in the population that is, or will likely become, suitable for statin usage, as well as in the doses and potency of prescribed statins. Indeed, randomized trial data have shown that atherosclerosis progression and coronary events are minimized when low-density lipoprotein cholesterol (LDL-C) is lowered to <70 mg/dL, and the re-evaluation of the desired LDL-C target is expected to substantially expand the population of statin-eligible patients.[2] Furthermore, the recent Jupiter trial has taught us that patients with elevated C-reactive protein, a surrogate marker of atherosclerosis-induced inflammation, can benefit from statin therapy even in the presence of LDL levels that might otherwise not justify pharmaceutical lipid-lowering interventions.[3] Finally, the versatile pleiotropic effects of statins are likely to broaden their indications far beyond lipid-lowering and prevention of cardiovascular disease.[4]

In our review[1] we emphasize that (i) statin potency and dose are both positively related to the magnitude of the anticipated clinical benefit; (ii) statin-related myopathy is a dose-dependent side effect; and (iii) although statin-related myopathy is a class effect, the relative risk appears to be higher with more potent statin molecules. Taken together, current evidence suggests that the additional clinical benefit achieved by high-dose and high-potency statin regimens rises in tandem with the anticipated risk of adverse events.[5,6] Impudently aggressive approaches when prescribing statins may therefore not represent the indicated strategy to optimize the benefit-risk ratio of these drugs.

The question inevitably arises: how far can we upsize statin regimens without jeopardizing our patients' safety, and who, among all statin-treated patients, are more likely to experience an adverse event? While the myopathic risk clearly varies among different statin molecules and doses, this risk should also be viewed through the spectrum

of patient-specific characteristics. When it comes to the risk of myopathy, patients, just like statins,[7] are not all the same. The definition of high-risk statin-receiving patients should therefore be emphasized, and the unique demographic, medical and genetic features that potentially increase a patient's risk of developing myopathy should be outlined. In our review, we focus on the differential risk of each patient, by underscoring possible predisposing and precipitating factors of statin-induced myopathy.[8] Conditions that increase the myopathic risk include advanced age, genetic factors, co-morbidities such as renal and hepatic dysfunction that augment statin bioavailability, neoplasias, heart failure, diabetes mellitus, familial hypercholesterolaemia and hypothyroidism, as well as hereditary metabolic syndromes such as familial mitochondrial encephalomyopathy. Concomitant medications may also increase the bioavailability of statins through pharmacokinetic interactions, or synergistically enhance their myotoxic potential through pharmacodynamic interactions, and thereby magnify the risk of clinically relevant myopathic manifestations.

The more we learn, the more we appreciate the importance of individual risk stratification and patient-tailored statin regimens, taking into account not only the risk related to statin potency and dose, but also the underlying risk factors that are unique for each patient. Statins have revolutionized prevention of cardiovascular disease; to prevent rare but potentially serious muscular adverse effects we need to identify individuals who are more susceptible to statin-induced myopathy and to adjust our clinical decision making accordingly.

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