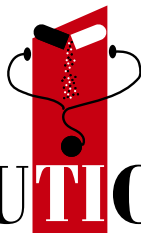




# THERAPEUTICS INITIATIVE



Evidence Based Drug Therapy

## Statins

### proven and associated harms

Therapeutics Letter #49 (Jul-Sept 2003) concluded that “Statins provide a cardiovascular and total mortality benefit for patients with clinically evident occlusive vascular disease (secondary prevention)” and Letter #77 (Mar-Apr 2010) concluded that “Statins do not have a net health benefit in primary prevention populations”, because they reduce coronary heart disease (CHD) serious adverse events (SAEs), but have no effect on total SAEs. This suggests that there are unidentified SAEs caused by statins that counterbalance the reduction in CHD SAEs.

Concerns about SAEs related to HMG-CoA reductase inhibitors (statins) were first raised in 2001, when cerivastatin was withdrawn from the market after being linked to over 100 deaths from muscle damage occurring at a rate much higher than other statins.<sup>1</sup>

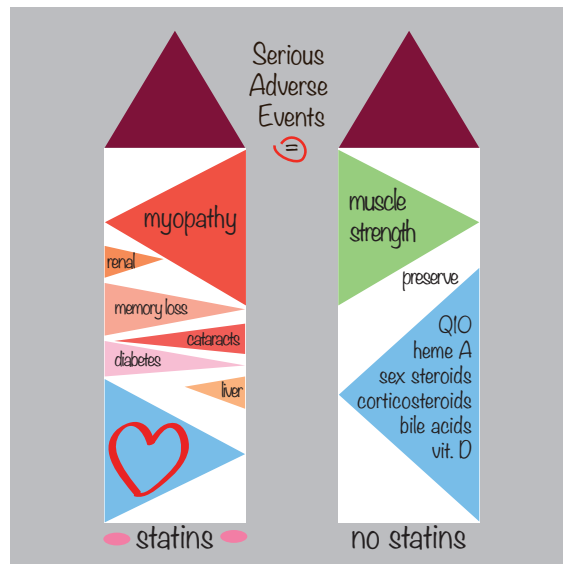
This Letter examines proven and associated harms with statin use. Proven harms are those that have been established in systematic reviews or randomized controlled trials (RCTs); associated harms are those identified from observational studies, case series and case reports.

#### How do statins work?

Statins inhibit the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase at an early stage of the mevalonate pathway. Cholesterol is generated by this pathway, but so are a number of other products with a pivotal role in bodily functions, such as coenzyme Q10, heme A, isoprenylated proteins, sex steroids, corticosteroids, bile acids, and vitamin D.<sup>1</sup> Statins reduce plasma cholesterol by inhibiting HMG-CoA reductase in the liver, but also inhibit this enzyme in tissues throughout the body.

#### Why aren't the harms of statins more commonly acknowledged?

First, most of the literature on statins has focused on the benefits. As a result awareness of statin harms is low<sup>2</sup>, and many specialists propound that statin harms are very unusual.<sup>3</sup> Second, the reported incidence of common statin effects, such as muscle pain and weakening, is low in randomized trials but higher in studies of real world use.<sup>1,4</sup> To some extent this is explained by use of a ‘run-in period’ in some statin RCTs when all patients are exposed to the drug prior to randomization and only those tolerating the drug are randomized.<sup>5</sup> Third, warnings about statin-related harm issued by the US FDA or Health Canada are slow to be released, and as with past advisories have little impact.<sup>6</sup>



### Canadian and US Advisories on statin-related harms

Since 2000 Health Canada has issued five ADR advisories related to statins: rhabdomyolysis and myopathy (January 2002),<sup>7</sup> Crestor and rhabdomyolysis (November 2004),<sup>8</sup> existing medical conditions which may increase risk of statin-related muscle problems (July 2005),<sup>9</sup> statins and memory loss (October 2005),<sup>10</sup> and statins and interstitial lung disease (October 2010).<sup>11</sup> On February 28, 2012, the US FDA revised statin labels, warning of the potential for “generally non-serious and reversible cognitive side effects (memory loss, confusion, etc.) and reports of increased blood sugar and glycosylated hemoglobin (HbA1c) levels”.<sup>12</sup>

#### Proven statin harms

##### Highest level of evidence: Systematic Reviews

The magnitude of harms from meta-analyses of RCTs are shown in Table 1.

Table 1. Statin harms demonstrated in meta-analysis of RCTs

Outcome	Statin Dose	RR or OR [95% CI]	ARI NNH	Ref.
Withdrawal due to adverse effects	High*vs low#	1.3 [1.2, 1.4]	2.1% 47 (3.4 yr)	13
Muscle damage (CK elevation >10x normal)	High*vs low#	10.0 [1.3, 78.0]	0.07% 1534 (3.4 yr)	13
Liver enzyme elevation	High*vs low#	4.8 [3.3, 6.2]	1.2% 86 (3.4 yr)	13
Newly diagnosed diabetes	High*vs low#	1.12 [1.04, 1.22]	1.0% 105 (4 yr)	14
Newly diagnosed diabetes	All doses	1.09 [1.02, 1.17]	0.4% 250 (4 yr)	15

\* High dose - simvastatin 80 mg, atorvastatin 40-80 mg.

# Low dose - simvastatin 20 mg, pravastatin 40 mg, atorvastatin 10 mg.

RR- relative risk, OR- odds ratio, ARI- absolute risk increase, NNH- number of people needed to treat to harm one person.

**Second level evidence: single RCTs**

Some statistically significant statin harms have been demonstrated in large RCTs. Others have been demonstrated in smaller RCTs designed to measure a specific effect: e.g. the 2012 RCT showing that simvastatin and pravastatin significantly decrease energy and increase fatigue after exertion compared with placebo<sup>16</sup> and the 2013 RCT demonstrating that simvastatin significantly attenuates cardiorespiratory fitness as compared to placebo in overweight and obese patients.<sup>17</sup> (See Table 2).

**Table 2. Statin harms demonstrated in single RCTs**

Outcome	Statin Dose	RR or OR [95% CI]	ARI NNH	Ref.
Hemorrhagic stroke	High*	1.7 [1.1, 2.6]	0.9% 108 (5 yr)	18
Cognition	Low	Decrease		19,20
Energy	Low	Decrease		12
Fatigue with exertion	Low	Increase		
Cardiorespiratory fitness	Low	Decrease		13
Sleep quality	Low	Decrease		21
Newly diagnosed diabetes	High#	1.25 [1.05, 1.49]	0.6% 167 (1.9 yr)	22

\*atorvastatin 80 mg, #rosuvastatin 40 mg.

**Associated statin harms**

**Third level evidence: Observational studies**

The magnitude of statin harms has also been estimated in large observational studies (see Table 3).

**Table 3. Statin harms supported by large observational studies**

Outcome	Statin Dose	RR or OR [95% CI]	ARI NNH	Ref.
Acute kidney injury	High* vs low	1.34 [1.25, 1.43]	0.06% 1700 (0.25 yr)	23
Acute renal failure	All doses vs no statin	1.6 [1.3, 1.9]	0.2% 450 (5 yr)	24
Moderate or serious liver dysfunction	All doses vs no statin	1.5 [1.4, 1.7]	0.7% 150 (5 yr)	24
Moderate or serious myopathy	All doses vs no statin	6.2 [5.2, 7.3]	1.0% 100 (5 yr)	24
Musculoskeletal conditions	All doses vs no statin	1.19 [1.08, 1.30]	2.1% 48 (4.4 y)	25
Cataracts	All doses vs no statin	1.3 [1.26, 1.37]	2% 50 (5 yr)	24

\* ≥ 10 mg rosuvastatin, ≥ 20 mg atorvastatin, ≥ 40 mg simvastatin

**Fourth level evidence: Case series and case reports**

A longer and growing list of harms is supported by case series and case reports. These are documented and referenced in the detailed analysis by Golomb and Evans and include peripheral neuropathy,

sexual dysfunction, gynecomastia, irritability, aggression, behaviour change, memory loss, depression, psychosis, interstitial lung disease, heart failure, Parkinson syndrome, lupus-like syndrome, dermatomyositis, other auto-immune syndromes, pancreatitis and others.<sup>1</sup>

**Muscle symptoms, the commonest statin adverse effect**

Patients taking statins can experience muscle pain, aches, soreness, weakness or fatigue, but these symptoms also occur in people not taking statins.<sup>4</sup> An approach to dealing with patients with statin related muscle symptoms is provided by Fernandez et al.<sup>26</sup> It is important to appreciate that falls in the elderly could be due to statin adverse effects on muscle. The incidence of muscle symptoms is low in RCTs<sup>4</sup> but higher in observational studies.<sup>27</sup> Muscle symptoms interfering with exercise and inhibition of cardiorespiratory fitness<sup>17</sup> are problematic because regular exercise is the best way for patients to prevent adverse cardiovascular events.<sup>28</sup> Minor muscle damage may be very prevalent as low level ultrastructural muscle damage was detectable in muscle biopsies from 10 of 14 patients taking statins with no muscle symptoms.<sup>29</sup> Greater damage was seen in patients with muscle symptoms, whether or not the creatine kinase was elevated, and whether treatment was continuing or had been stopped for varying lengths of time. This suggests that the damage is not readily reversible.<sup>30</sup>

**Clinical Implications**

Statin work by inhibiting a critical enzymatic pathway and thus have many potential effects in addition to the reduction of serum cholesterol. **The full spectrum of statin related harms and their magnitude is still largely uncertain.** However, from this analysis it is clear that the magnitude of statin harms is greater with high doses than with low doses and that the added benefits of high doses is unlikely to exceed the magnitude of the harms in most if not all clinical settings.<sup>14</sup> Even for lower doses the magnitude of harms appears to be in the range of 1-2%, a range similar to the benefits of statins for primary prevention. Physicians must be vigilant in order to detect statin adverse effects as many of them are subtle. When statins interfere with exercise, the benefits of exercise are undermined.

**Conclusions**

- The action of statins to reduce many compounds in addition to cholesterol is problematic.
- Harms with statins are often subtle, usually dose related, sometimes serious and require vigilance to detect.
- The magnitude of most statins harms remains uncertain at this time.
- It is essential to weigh the potential benefits and the potential harms in all patients taking or being considered for statin therapy.

For the complete list of references go to [www.ti.ubc.ca/letter89](http://www.ti.ubc.ca/letter89)

The draft of this Therapeutics Letter was submitted for review to 60 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

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