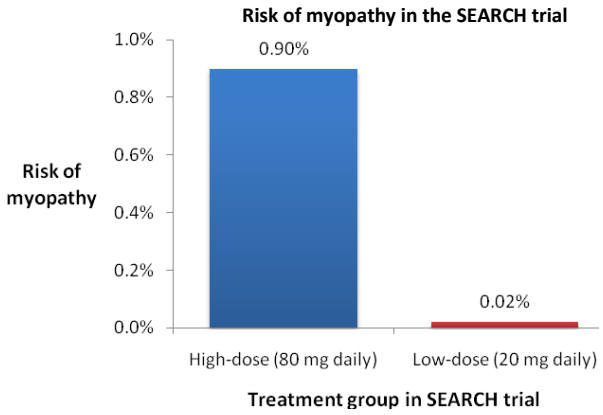
iDiS PEARL: Prompt Evidence Assessment and Review of the Literature

Rethinking the role of simvastatin: recent cautions from FDA

The clinical issue: Based on findings from a large randomized trial, the FDA has recommended avoiding the use of simvastatin at high doses (80 mg per day) and has added new contraindications for its use with other medications, even at lower doses. [1]

The SEARCH trial was a randomized, double-blind study[2] that assigned 12,064 post-MI patients to receive either high-dose (80 mg) or low-dose (20 mg) simvastatin. The primary outcome of major vascular events occurred in fewer patients in the high-dose group (6% relative risk reduction), although this advantage was not statistically significant. However, **myopathy occurred significantly more often in the high-dose group** (see Figure). (Myopathy was defined as unexplained muscle weakness or pain with a CK > 10 times the upper limit of normal.) It was most common in the first 12 months of therapy, as well as in older patients and women. The risk was approximately doubled in patients concurrently using diltiazem and simvastatin, at either simvastatin dose. Although the more extreme problem of rhabdomyolsis was uncommon, it occurred in 7 patients in the high-dose but none in the low-dose group.



The warnings: Based on this data, the FDA issued the following safety warnings for simvastatin alone or in combination with other drugs (e.g. as Vytorin and Simcor):

Simvastatin dose	DO NOT use in patients :
80 mg daily	unless they have been taking this dose for at least a year without muscle symptoms
≥ 20 mg daily	who are taking amlodipine or ranolazine
≥ 10 mg daily	who are taking amiodarone, verapamil, or diltiazem
Any dose	who are taking certain antifungals (itraconazole, ketoconazole, posaconazole), macrolide antibiotics (erythromycin, clarithromycin, telithromycin), HIV protease inhibitors, nefazodone, gemfibrozil, cyclosporine, or danazol.

Practice implications: At doses under 80 mg, simvastatin remains a useful, safe, and affordable drug for lowering cholesterol in many patients. For those who need LDL-lowering that would require a high dose of simvastatin, or are taking potentially interacting medications, many alternatives can achieve equivalent LDL reductions and do not seem to cause the same risk of myopathy. These are summarized below[3]:

Percentage LDL reduction by statin and dose

	Daily dose of statin (mg)					
Drug	**5**	**10**	**20**	**40**	**60**	**80**
simvastatin (Zocor or generics)	**23%**	**27%**	**32%**	**37%**	-	**42%***
rosuvastatin (Crestor)	**38%**	**43%**	**48%**	**53%**	-	-
atorvastatin (Lipitor)	-	**37%**	**43%**	**49%**	-	**55%**
lovastatin (Mevacor or generics)	-	**21%**	**29%**	**37%**	**42%**	-
pravastatin (Pravachol or generics)	-	**20%**	**24%**	**29%**	-	**33%**
fluvastatin (Lescol)	-	-	**21%**	**27%**	-	**33%**

Expected to lower LDL by ≥ 50% | Expected to lower LDL by 40-50% | Expected to lower LDL by < 40% | - Not available at this dose | New use should be avoided

More details on use of statins can be found in the iDiS monograph on lipid-lowering drugs, available at www.rxfacts.org.

References: 1. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm258338.htm; 2. Lancet, Volume 376, Issue 9753, Pages 1658 - 1669, 13 November 2010; 3.Adapted from Law et al BMJ 2003;326(7404):1423

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These are general recommendations only; specific decisions should be made by the treating physician based on an individual patient's clinical condition.

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