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THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

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Statin's benefit for secondary prevention confirmed.

What is the optimal dosing strategy?

Introduction

Letters # 24, 27 and 42 recommended statin therapy for patients with ischemic heart disease (secondary prevention) based on 3 relevant randomized controlled trials (RCTs): 4S[1], CARE[2], and LIPID[3]. Letter #48 pooled the data from the 5 mostly primary prevention trials and concluded that statins have not been shown to provide an overall health benefit in patients without clinically evident atherosclerosis. This Letter summarizes the 4 latest secondary prevention statin trials and discusses 3 different dosing strategies.

Lescol Intervention Prevention Study (LIPS)[4]

LIPS studied the effect of 80 mg of fluvastatin compared to placebo in 1677 patients (total cholesterol 3.5-7.0 mM) with coronary blockage following successful completion of a percutaneous coronary intervention. Total myocardial infarctions, RR 0.69 [0.47–1.01], and total mortality, RR 0.73 [0.48–1.10] were not statistically significantly lower with fluvastatin than placebo. Stroke outcomes and total serious adverse events were not reported.

PROSPER[5] (described in Letter #48)

Pravastatin, 40 mg, reduced total myocardial infarction or total stroke in the 2565 elderly (70-82 years) secondary prevention patients (total cholesterol, 4.0–9.0 mM), RR 0.80 [0.68–0.94], ARR 4.3%, NNT 23 for 3.2 years.

GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE)[6]

GREACE compared the effect of structured care using a titrated dose of atorvastatin with 'usual' community care in 1600 patients (LDL cholesterol >2.6 mM) with recent myocardial infarction or >70% stenosis of at least one coronary artery. In the structured care group atorvastatin 10 mg/day was increased to 80 mg if necessary to achieve an LDL of <2.6 mM. Structured care reduced total myocardial infarction or stroke, RR 0.47 [0.34–0.65], ARR 7.0%, NNT 14 for 3 years. Total mortality was also reduced, RR 0.58 [0.35–0.95], ARR 2.1%, NNT 48 for 3 years. Total serious adverse events were not reported.

Heart Protection Study (HPS)[7]

HPS, the largest statin trial, compared simvastatin, 40 mg daily, with placebo in 20,536 patients (86% secondary prevention, total cholesterol >3.5 mM). Simvastatin reduced total myocardial infarction or stroke, RR 0.75 [0.70–0.80], ARR 4.4%, NNT 23 for 5 years. Total mortality was also reduced RR 0.87 [0.81–0.94], ARR 1.8%, NNT 56 for 5 years. Total serious adverse events were not reported. The benefit of simvastatin was independent of baseline cholesterol and independent of the magnitude of the simvastatin-induced reduction in LDL. Patients with baseline LDL <2.6 mM had a similar benefit to those with baseline LDL >2.6 mM.

HPS was unusual in having a pre-randomization period in which 32,145 recruited patients were treated with simvastatin 40 mg for 4 to 6 weeks. Thirty six percent (11,609) of these patients were dropped from the study for various reasons: poor compliance, patient choice, side effects etc. Because large numbers of problematic patients were excluded, the HPS results cannot be used to predict the safety and tolerance of simvastatin in the general population.

These 4 trials reconfirm the benefit of statins for patients with elevated cholesterol and coronary disease and **expand the benefit to patients with clinically evident occlusive coronary, cerebral or peripheral vascular disease and a total cholesterol >3.5 mM.** Despite the lack of reporting of total SAEs in these trials, one measure of overall health benefit, total mortality, was reduced, pooled RR 0.84 [0.79–0.88], ARR 2.1%, NNT 48 for 3 to 5 years.

A question to us about Letter #48: **What is the evidence of benefit for primary prevention in women?**

There were 10,990 women in the primary prevention trials (28% of the total). Only coronary events were reported for women, but when these were pooled they were not reduced by statin therapy, RR 0.98 [0.85-1.12]. Thus the coronary benefit in primary prevention trials appears to be limited to men, RR 0.74 [0.68-0.81], ARR 2.0%, NNT 50 for 3 to 5 years.

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What is the optimal statin dosing strategy?

RCTs comparing the morbidity and mortality of different statin dosing strategies have not been conducted. Clinical dosing strategies can be indirectly inferred from the 11 existing RCTs. Three of a number of possible dosing strategies are discussed below.

"Fixed dose" strategy

Eight of eleven RCTs[2-5,7,8] tested a single dose of statin. A "fixed dose" strategy based on these trials would employ the daily dose used in the trials: atorvastatin 10 mg, fluvastatin 80 mg, pravastatin 40 mg, or simvastatin 40 mg. ***Advantages:*** based on specific RCT evidence, limited or no cholesterol testing required, includes all patients. ***Disadvantages:*** a fixed dose may be insufficient for some and excessive for other patients.

"LDL target" strategy

Three RCTs treated to target based on cholesterol testing: 4S,[1] AFCAPS[8] and GREACE[6]. In 4S the target was a total cholesterol <5.2 mM (LDL <3.8 mM). In AFCAPS the target was an LDL <2.8 mM. In GREACE the target was an LDL of <2.6 mM. A dosing strategy based on these trials would titrate the dose to an LDL target. ***Advantages:*** consistent with lipid guidelines in the US/Canada[9] (LDL <2.6 mM) and UK/Europe[10] (LDL <3.0 mM), prevents excessive LDL lowering if the dose is minimized to just achieve the target. ***Disadvantages:*** optimal target is unknown, requires more LDL testing and higher statin doses, patients with baseline LDL <2.6 mM, who were proven to benefit in HPS[7], would be excluded.

"Average cholesterol reduction" strategy

The average reduction from baseline in total cholesterol for the different statins was between 18 and 25% for 10 of the 11 RCTs. The one exception is GREACE (36% reduction).[6] Daily doses of statin required to achieve the middle of this range, a 22% reduction in total cholesterol, are approximately: fluvastatin 40 mg, pravastatin 20 mg, lovastatin 20 mg, simvastatin 10 mg, atorvastatin 5 mg or rosuvastatin 2.5 mg.[11] ***Advantages:*** reduced statin doses and costs, possible reduced risk of dose-related toxicity, includes all patients. ***Disadvantages:*** necessitates some testing of total cholesterol.

Regardless of what dosing strategy is chosen for a particular patient, **choosing higher strength statin tablets (lower price/mg) and tablet splitting, can be used to reduce the daily cost (see Table).**

What is needed?

Large RCTs comparing different statin dosing strategies for secondary prevention of cardiovascular disease are clearly needed. These trials should as a minimum report the following outcomes: total mortality, cardiovascular serious adverse events, other serious adverse events and total health related costs.

Conclusions:

- **Statins provide a cardiovascular and total mortality benefit for patients with clinically evident occlusive vascular disease (secondary prevention) and a cholesterol of >3.5 mM.**
- **Large RCTs are required to test different statin dosing strategies for secondary prevention before making firm recommendations.**

Table. Statins, daily doses and cost comparisons

Drug	Brand Name (formulation)	Possible daily doses (mg)	Cost per dose+
Atorvastatin	Lipitor (tablets)	2.5*, 5*, 10, 20, 40, 80	$0.43, 0.86, 1.71, 2.14, 2.30, 2.30
Fluvastatin	Lescol (capsules)	20, 40, 80	$0.82, 1.15, 2.30
Lovastatin	Mevacor, generic (tablets)	10*, 20, 40, 80	$0.59, 1.17, 2.15, 4.30
Pravastatin	Pravacol, generic (tablets)	10, 20, 40, 80	$1.02, 1.20, 1.45, 2.90
Simvastatin	Zocor, generic (tablets)	5, 10, 20, 40, 80	$0.67, 1.33, 1.65, 1.65, 1.65
Rosuvastatin	Crestor (tablets)	2.5*, 5*, 10, 20, 40	$0.37, 0.73, 1.46, 1.82, 2.13

* requires cutting of tablets to achieve these doses; + based on 2003 PharmaNet data or wholesale cost plus 7%

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This Letter contains an assessment and synthesis of publications up to September 2003. We attempt to maintain the accuracy of the information in the Therapeutics Letter by extensive literature searches and verification by both the authors and the editorial board. In addition this Therapeutics Letter was submitted for review to 45 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.