



The sorry saga of the statins in New Zealand – pharmacopolitics versus patient care

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In the past five years, the average patient requiring an HMG-CoA reductase inhibitor or ‘statin’ in New Zealand has suffered at the hands of the Pharmaceutical Management Agency Ltd (PHARMAC) and drug companies. PHARMAC operates in a monopsony (a market with one buyer). With its focus directed on a narrow financial bottom line (the pharmaceutical bill in the short term), it has played reference-pricing dominoes with little consideration for the broader, or long-term concerns of healthcare. The drug companies, rather than making a united stand in favour of best evidence, have competed to outmanoeuvre each other for market share.

In essence, PHARMAC repeatedly changed the reference-priced (subsidised) statin as companies did deals with it. For short-term, narrow-focussed financial reasons, patients were forced to change from simvastatin or pravastatin to fluvastatin, then atorvastatin, and for many, back to simvastatin.

Little consideration was given, by either PHARMAC or the drug companies, to the effects of “switching”. There was little consideration of evidence-based medicine. There was little consideration of the relative pharmacological advantages of the individual drugs (adverse effects, drug interactions, etc). There was little consideration of the flow-on costs of this simplistic pricing strategy. As long as short-term savings to the pharmaceutical ledger were apparently being made, PHARMAC could hide behind its oft-quoted crowd pleaser “a saving here will allow more money to be spent there”.

Let us consider the history of this debacle. The 4S study of simvastatin in secondary prevention provided firm evidence that statins actually save lives in patients with existing ischaemic heart disease. Other studies with pravastatin quickly followed.¹ The WOSCOPS trial showed reduced mortality and morbidity rates with pravastatin in the primary prevention of cardiovascular disease.² Both the CARE and LIPID trials, also with pravastatin, showed improved outcomes for secondary prevention of cardiovascular disease.^{3,4} Statins became hot property.

PHARMAC rightly realised that the widespread use of statins could result in a financial blow-out. The Pharmacology and Therapeutics Advisory Committee (PTAC) subcommittee of lipid experts concluded that “ideally the statins should be subsidised, based on their ability to modify absolute risk, or reduce total mortality”. Simvastatin and pravastatin had the greatest evidence base, and were cheaper per percentage reduction in cholesterol than fluvastatin. Yet PHARMAC stated that “their lipid experts view that there is sufficient evidence that all statins have the same or similar effect”. In December 1996, fluvastatin became the reference-priced statin.

On the basis of evidence, the reference-priced drug should have been simvastatin or pravastatin. There were no proven morbidity or mortality data supporting fluvastatin. On the basis of pharmacology, pravastatin had some advantages. It was less lipid

soluble than the other statins, giving it some potential advantages in terms of muscle toxicity and drug interactions.⁵ Simvastatin, which is metabolised by CYP3A4, has problems with drug interactions, and also a notable interaction with grapefruit juice. The area under the plasma concentration-time curve of simvastatin can be several times larger when it is taken with grapefruit juice, through inhibition of presystemic metabolism.⁶ This interaction does not occur with pravastatin.⁷ On the basis of pharmacology, pravastatin was arguably the statin of choice.

But, as already mentioned, fluvastatin became the reference-priced drug. This had the immediate result that doctors were forced to shift the majority of their patients from the statin on which they were stabilised to fluvastatin, or inform them that they would have to pay to remain on their original drug. The use of pravastatin declined, and on 1 June 2002 it was delisted from the Pharmaceutical Schedule (ie, it is no longer funded). No process was put in place to monitor, prospectively, for any adverse effects, and the inevitable extra workload forced on practitioners to facilitate such switching was seen as only a minor problem. PHARMAC expressed pride in the process.⁸

Fortunately, an independent audit occurred. Professor Jim Mann from Dunedin published observational data suggesting that the switch to fluvastatin resulted not only in deterioration in control of lipid concentrations in most patients,⁹ but also a significant increase in the frequency of thrombotic vascular events compared to the previous six months of simvastatin therapy ($p < 0.001$).¹⁰ This was not surprising, because fluvastatin, in its suggested dosage range, operates at a lower part of the dose-response curve than the other statins, and the same lowering of lipids in the same number of people could not be expected.⁹

The deficiencies of fluvastatin were so marked that they were quickly perceived, not only by practitioners, but presumably also by PHARMAC, who raced to reference price another, more powerful, statin. The statin chosen was atorvastatin – the most potent, and in the doses selected, the most powerful lipid-lowering agent available at the time. The problem with atorvastatin was that, like fluvastatin, its evidence basis was lacking compared with simvastatin and pravastatin. Pharmacologically, it did not quite have the advantages of pravastatin, but the potential for interactions was quantitatively less than for simvastatin.⁷

The reason atorvastatin was chosen was not actually related to any of the above, but to a cross-subsidisation deal between PHARMAC and Parke-Davis (now Pfizer), distributor of atorvastatin. Parke-Davis was keen to enter the lipid market, and was prepared to discount quinapril, its ACE inhibitor, substantially to get the nod for atorvastatin. As a tickler, Parke-Davis agreed to a ‘capped budget’ for atorvastatin, meaning that if sales increased above a certain point, they (Parke-Davis) would absorb this cost. This is a form of risk-sharing, and serves as an insurance for PHARMAC against cost blow-outs. The deal went through, and quinapril became the reference-priced ACE inhibitor, along with cilazapril. The consequent switching of ACE inhibitors from enalapril, the market leader, to these newer ‘prils’ is another sorry saga, but outside the brief of this article.

Cross-subsidisation deals can make sense in a hard business world, but clearly they render rational discussion difficult or impossible when it comes to determining the cost benefits of an individual drug in the world of medical care.

The effect of the reference pricing of fluvastatin and then atorvastatin was initially predictable. There was a wholesale shift from the evidence-based statins to either of these drugs, and for some patients a double change, through fluvastatin to atorvastatin. With time, however, sales of fluvastatin began to drop off as doctors realised that this drug was not very effective in lowering cholesterol. Atorvastatin sales increased more than expected and surpassed the cap agreed upon by PHARMAC and Parke-Davis.

Meanwhile, Merck Sharp and Dohme (MSD), makers of simvastatin, were able to bring the price of simvastatin (Zocor) down because its patent had expired. This set a new reference price for the group, which PHARMAC grasped with relish. Seeing the possibility that other generics of simvastatin might challenge their market after expiry of patent in January 2002, MSD began long and complicated negotiations with PHARMAC. As a result, a deal was struck in which MSD reduced the price of simvastatin further, with the quid pro quo for PHARMAC being that other generics would not be introduced until at least 2006.

On 1 April (!) 2002, with the price of simvastatin now very low and in response to considerable external pressure, PHARMAC was able to remove the special authority requirements, thereby increasing access to this class of medicines. PHARMAC is to be commended for this. Pfizer's special arrangement with PHARMAC for the pricing of atorvastatin persists until April 2004, at which point this statin will also be reference priced, presumably against simvastatin. To limit the numbers using atorvastatin, and to reduce the cost burden to the company (currently atorvastatin sales exceed its cap by many \$millions), the use of this drug remains under 'special authority'. Fluvastatin was deemed unviable for our market by the company that produced it, and was 'delisted' in New Zealand in November 2002 (Lescol) and on 1 February 2003 (Vastin). These moves effectively give the market to simvastatin, with the inevitable new round of switching.

As if this is not complicated enough, MSD now promotes simvastatin under the name Lipex, rather than Zocor. The drug is identical. The name was changed because the price of Zocor in New Zealand had become so low in international terms that comparisons might be made, and there was a risk of parallel importing from New Zealand to other less regulated countries.

Recently, the results of the Heart Protection Study, the largest trial of statin therapy, confirmed the mortality and morbidity benefit of simvastatin in patients at high risk of coronary heart disease.¹¹ This trial showed benefit regardless of age, gender or baseline cholesterol, and that the drug was well tolerated.

There is still no evidence for either fluvastatin or atorvastatin that is comparable to that for simvastatin or pravastatin in terms of improved clinical outcomes in primary and secondary prevention of cardiovascular heart disease. High doses of both fluvastatin (40 mg twice daily) and atorvastatin (80 mg daily) have been studied in the more specific clinical settings of post angioplasty and post acute coronary syndrome in the FLARE¹², AVERT,¹³ and the MIRACL¹⁴ studies. These studies showed some clinical benefits with treatment, but none of them showed clinical benefit in all areas (death, myocardial infarction, intervention rates).

At the end of the day, this saga has been a triumph for the short-term, narrow-focussed financial imperative, and a disaster for the medical practitioner, medical

education, community pharmacists and, most importantly, the patient. Decisions made have flown in the face of evidence-based medicine and conventional teaching of therapeutics. The message imparted is that immediate savings in pharmaceutical spending are the primary concern; long-term savings in the broader health sector, health outcomes, pharmacological principles, teaching principles, practitioner workloads, and good patient care matter less.

It is a tenet in the teaching of therapeutics not to rock the boat. If a drug is working for the patient, make an alteration only with good reason. It often takes a great deal of time and effort to achieve concordance with the patient on what is the right drug for them, at the right dose, and in the right combination with other drugs. Changing from one drug to another in the same class at assumed equivalent doses, should not be undertaken lightly. It is likely to result in therapeutic failure in some patients (through under-dosage), appearance of new side effects in others (through over-dosage, or particular drug idiosyncrasies), and drug interactions with varied effects in others. History abounds with examples of the dangers associated with assuming a 'class effect', eg, the withdrawal of the β -blocker practolol because of serious though rare side effects, various non-steroidals such as benoxaprofen, and the calcium antagonist mibefradil.¹⁵

Interestingly, PHARMAC pays little heed to its own decision criteria for amendments to the Pharmaceutical Schedule. It is difficult to see how its decisions improved overall budgetary impact, had clinical benefits over risks (unmonitored), or met the needs of Maori and Pacific people, who are particularly prone to cardiovascular disease. The problem with the PHARMAC model is that switching can occur next month, next year, the year after, or whenever a new deal can be struck. Something needs to be done to stem this tide. It is our contention that the incentives under which PHARMAC operate must change, from cost-focussed to health-focussed.

Whether or not the actions of PHARMAC can be considered ethical is open to question. On one hand, the Medical Council of New Zealand states in its Ethical Guidelines for doctors in an environment of competition or resource limitation, "A doctor's primary responsibility is to his or her patient. The responsibility is not only to provide the best care possible within resources available but also to make clear to any patient to whom care of proven effectiveness is being denied by any funder or provider, that what is being provided is not optimal care, by generally agreed standards of medical practice."¹⁶ On the other hand, the Chairman of PTAC argued that "medical professionals tend to weigh too heavily the ethical responsibility they have to the individual patient, but of equal importance is the competing duty of care to the society and the taxpayer".¹⁷

The history of the health reforms in New Zealand has often been one of silence – silence from those who know things are wrong, but will not say so. We need to be better advocates for our patients. As John Ralston Saul, the Canadian philosopher–author said, "Our primary obligation as citizens is to speak up and disagree."

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References:

1. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383–9.
2. Shepherd J, Cobbe SM, Ford I, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995;333:1301–7.
3. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med* 1996;335:1001–9.
4. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. *N Engl J Med* 1998;339:1349–57.
5. Hamelin BA, Turgeon J. Hydrophilicity/lipophilicity: relevance for the pharmacology and clinical effects of HMG-CoA reductase inhibitors. *Trends Pharmacol Sci* 1998;19:26–37.
6. Lilja JJ, Kivisto KT, Neuvonen PJ. Grapefruit juice-simvastatin interaction: effect on serum concentrations of simvastatin, simvastatin acid, and HMG-CoA reductase inhibitors. *Clin Pharmacol Ther* 1998;64:477–83.
7. Lilja JJ, Kivisto KT, Neuvonen PJ. Grapefruit juice increases serum concentrations of atorvastatin and has no effect on pravastatin. *Clin Pharmacol Ther* 1999;66:118–27.
8. Braae R, McNee W, Moore D. Managing pharmaceutical expenditure while increasing access. The pharmaceutical management agency (PHARMAC) experience. *Pharmacoeconomics* 1999;16:649–60.
9. Thomas MC, Mann J, Williams S. The impact of reference pricing on clinical lipid control. *NZ Med J* 1998;111:292–4.
10. Thomas M, Mann J. Increased thrombotic vascular events after change of statin. *Lancet* 1998;352:1830–1.
11. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20 536 high-risk individuals: a randomised placebo-controlled trial. *Lancet* 2002;360:7–22.
12. Serruys PW, Foley DP, Jackson G, et al. A randomized placebo-controlled trial of fluvastatin for prevention of restenosis after a successful coronary balloon angioplasty; final results of the fluvastatin angiographic restenosis (FLARE) trial. *Euro Heart J* 1999;20:58–69.
13. Pitt B, Waters D, Brown WV, et al. Aggressive lipid-lowering therapy compared with angioplasty in stable coronary artery disease. Atorvastatin versus Revascularization Treatment Investigators. *N Engl J Med* 1999;341:70–6.
14. Schwartz GG, Olsson AG, Ezekowitz MD, et al. Effects of atorvastatin on early recurrent ischaemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. *JAMA* 2001;285:1711–8.
15. Furberg CD, Herrington DM, Psaty BM. Are drugs within a class interchangeable? *Lancet* 1999;354:1202–4.
16. Medical Council Ethical Guidelines for doctor's duties in an environment of competition or resource limitation. *NZ Med J* 2000;113:65–6.
17. Pharmacology Management Agency Ltd (PHARMAC) Drug Scene. Views: It's time we doctors took a new, fresh look at our ethics. Sept 1997.