ABSTRACT

Simvastatin 10mg (Zocor Heart Pro®) became available for purchase under the supervision of a pharmacist (i.e. as a ‘P’ medicine) in the UK in 2004 and remains the only statin available for self medication worldwide.

This ‘switch’ from prescription only (POM) status was regarded as a landmark for self care, principally because the aim, for the first time, was self-management of risk: in this case moderate risk of a cardiac event in the next 10 years. Despite backing from specialists in cardiovascular diseases, the move was controversial, attracting adverse comments from general practitioners (GPs) in particular, and it consequently received a nervous and lukewarm response from pharmacists. Several aspects of the switch were criticised: the dose was thought too low; the evidence-base in the target population was said to be inadequate; the lack of mandated cholesterol testing worried others and some simply considered the safety profile of statins as unsuitable for self care.

Now, 6 years on, usage of simvastatin for self care is very low, but statin use on prescription has continued to expand in the UK and elsewhere. This case study examines the rationale which drove the switch model and the reasons why, in the light of prevailing guidelines, the switch faced such opposition and criticism. The possible lessons to be learned and applied to future complex switch proposals are also discussed.

Key words: Simvastatin, Zocor Heart Pro®, cardiovascular risk, heart attack, prevention, risk management, statins, self medication, POM to P, Switch, OTC.

INTRODUCTION

The story of the ‘POM to P switch’ (reclassification from prescription only to pharmacy status) of simvastatin 10mg began several years before the patent protection of the parent drug was due to end. In early 2003 Zocor (simvastatin in tablet strengths from 10mg to 80mg) was the most prescribed drug in the world, but imminent patent expiry in markets including the UK would signal the substitution, almost overnight, of generic simvastatin for the bulk of prescriptions.

It is not unusual for ‘lifecycle management’ of successful prescription drugs to be an afterthought when patent expiry threatens, however it would be unfair to characterise the switch of simvastatin in that way. Firstly, Merck & Co. (the originators of simvastatin) had formed a joint venture with Johnson & Johnson, a leading consumer pharmaceutical company, many years previously in the US, and 10 years earlier had expanded this to Europe (as Johnson...
& Johnson.MSD). The principal purpose of this joint venture was to manage the creation of consumer pharmaceutical medicines from candidate prescription drugs in the Merck portfolio. Secondly, efforts in the US to switch lovastatin 20mg (Mevacor®, an earlier Merck & Co. statin, never launched in most of Europe) to self-medication status, had been underway for some years and had even been the subject of an unsuccessful FDA advisory committee meeting in 2000. However the bar for changing some medicines to self-medication status appears to be set higher in the US than in Europe, partly because there is no ‘P’ category to legislate for the intervention of a pharmacist, leaving the consumer to make correct choices on the basis of labelling alone.

The possibility that statins might be suitable ‘P’ medicines had been voiced in Europe, notably in a European Commission sponsored AESGP report in 2002. In the UK, government pronouncements on increasing access to medicines, backed by targets for POM to P switches, created a positive environment in which to discuss new and possibly radical proposals for self care.

HISTORICAL PERSPECTIVE – STATINS IN 2003/2004

It is instructive to consider proposals for self care in the context of prescribing practice prevailing at the time. In the UK in 2003, the use of prescription statins was in a state of flux. The ‘cholesterol controversy’ (as described eloquently by Tobert in a 2003 review) had arguably raged hotter and longer in the UK than elsewhere. Consequently growth in prescription usage of statins had lagged behind that in other countries. It was only when the publication of landmark studies such as the Scandinavian Simvastatin Survival Study (4S) put the basis for statin use in secondary prevention of coronary disease beyond serious debate, that statin usage really ‘took off’ at all. The publication of the Joint British Societies’ guidelines in 1998, subsequently endorsed in the National Service Framework (NSF) for Coronary Heart Disease (CHD) in 2000 finally gave unequivocal support and guidance for statin use in the National Health Service (NHS) and provided the impetus to steepen the trajectory of prescription use (Figure 1).

**Figure 1: Prescriptions for lipid lowering drugs, 1981 to 2007, England**

![Prescriptions for Lipid Lowering Drugs](source: Office for National Statistics (2008))
Nevertheless, it is important to remember exactly what the recommendations were for GPs in the early 2000s. The NSF for CHD restricted the prescription of statins in the NHS to those individuals who had already suffered a coronary event (i.e. secondary prevention) and recommended primary prevention only for those at 30% or greater risk of a coronary event in the next 10 years (i.e. carrying a risk equivalent to those with a history of CHD events). As well as these high levels of risk, individuals also had to have a total cholesterol concentration $\geq 5.0$ mmol/l to qualify for a statin prescription. However, there was a clear recognition in the 1998 JBS guidelines that there was good evidence to support statin usage at lower levels of risk and a recommendation that treatment should be extended down to those at 15% risk over 10 years, ‘as resources permit’.

In 2003 the JBS guidelines were in the process of revision (although they were not to appear in full as JBS2 until late 2005) and new thinking on CHD risk was prevalent. There were several important relevant principles becoming widely accepted, which included:

- The acceptance that CHD, cerebrovascular disease and disease affecting other parts of the vascular tree all share endothelial dysfunction as a common patho-physiological mechanism. It follows that to separate risk artificially by end organ damage is unhelpful, and we should instead consider cardiovascular disease (CVD) risk as a whole.

- The recognition that ‘lifetime’ risk of CVD accumulates as an ‘S’ shaped curve with the upward slope beginning at around 45 years in men and 55 years in women. This led to suggestions that absolute risk in those below 60 years of age should be projected forward to risk at 60 years to correct for the underestimate that would otherwise occur.

- The recognition that the ‘average’ total cholesterol (TC) in a population may not be the best guide to setting a threshold for treatment. In fact removing the 5.0mmol/l threshold for statin treatment entirely would increase the numbers of UK patients qualifying for treatment very little at high levels of risk and modestly at lower levels of risk.

- Importantly, strong evidence had accumulated (most recently from the Heart Protection Study) to support the contention that reduced risk of cardiovascular events and reduction of Low Density Lipoprotein cholesterol (LDL-C) were related in an approximately linear fashion, with no apparent lower threshold level. So the proportional reduction in the event rate was largely independent of the starting LDL-C level. This in turn meant that the level of CVD risk, rather than cholesterol level, should determine the need for cholesterol lowering intervention. Furthermore the target level for TC and LDL-C needed to be much lower than previously set to achieve optimal risk reduction in high risk individuals.

The JBS2 guidelines would ultimately encompass all of these principles to some extent, but for the critical period around the launch of simvastatin 10mg for self-medication, there was an important divergence between published practice guidelines and contemporary expert opinion. Inevitably, the model for supply of Zocor Heart Pro had to rely more heavily on the latter than the former, if it was not to become quickly outdated.
THE ZOCOR HEART PRO (ZHP) MODEL

Johnson & Johnson. MSD met with the Medicines Control Agency (now the Medicines and Healthcare products Regulatory Agency – MHRA) in early 2003. The agency encouraged the company to develop a proposal and remained open to discussion, adopting a collaborative stance throughout the time leading up to submission.

The company began a period of intense consultation with opinion leaders in lipid disorders and cardiovascular medicine, including GPs with a specialist interest in the subject. A broad consensus emerged that an appropriate self-medication model for a statin should:

- Target a population at a level of risk below that designated in the JBS guidelines as ‘high’ and therefore ultimately suitable for NHS treatment, but well within the range at which benefit had been shown in endpoint studies. A 10 year risk of a first CHD event of 10-15% met these criteria.

- Select this moderately ‘at risk’ population in a pharmacy setting in the simplest way so as to reach the maximum number of people that might benefit. The model must allow people at very low or high risk to be excluded and advised appropriately.

- Offer a comprehensive risk-reduction strategy addressing all modifiable risk factors in the selected group to produce the greatest benefit.

It was recognised that these were not easy propositions to deliver since they required people to understand both concepts of risk, and the extent to which interventions could reduce that risk.

RISK ASSESSMENT

General Principle

Until that time, cardiac risk assessment had been carried out by physicians and involved a comprehensive assessment of all individual risk factors, including a full lipid profile. This was because these efforts were directed towards identifying very high-risk individuals. The difficulty and cost of adopting this approach at lower levels of risk was apparent and had led some to advocate an age based risk assessment (e.g. at age 50 years) using normalised population levels of TC, LDL-C and High Density Lipoprotein cholesterol (HDL-C) to identify those at above moderate risk (>15% 10 year risk of CHD events) for comprehensive screening and assessment.

The expert panel felt that selecting populations for self-medication should also be based on absolute risk, but that there was no need to duplicate the doctor-led model precisely, since the aims were different. Accordingly:

- Because self-medication does not rely on constrained resources there is no need to apply thresholds designed to prioritise the use of those resources. Therefore those eligible for self-
medication should be selected solely on the evidence that they will benefit from the chosen intervention.

• There is good evidence that lowering LDL-C with statins in those at moderate risk (i.e. 10-15% 10 year risk) of CHD can substantially reduce their risk regardless of the starting level of cholesterol. Therefore, if individuals can be assigned reliably to a moderate absolute risk category there is no need to have a full cholesterol status before starting treatment.

This latter point was significant because cholesterol screening was not readily available in UK pharmacies (then or now) and a requirement for prior screening would have been an important barrier to self-management. However the panel did feel that monitoring cholesterol response to treatment was useful and had the added potential benefit of identifying rare unrecognised dyslipidaemias.

Assigning CHD Risk in Pharmacy

The major risk factors for CHD (excluding LDL-C cholesterol status) that influence decisions to lower LDL-C, are given in Table 1.

**Table 1: Major independent risk factors (excluding LDL-C) for CHD influencing selection for LDL-C lowering**

- Smoking
- High Blood Pressure
- Diabetes (regarded as a risk equivalent to existing CHD disease)
- Family History of premature CHD in a first degree relative (male<55years, female<65years)
- Age (men 45 years or older, women 55 years or older)

Adapted from: National Cholesterol Education Program, Adult Treatment Panel III

People with known heart disease, known familial hypercholesterolaemia and other familial dyslipidaemias, hypertension and diabetes were excluded from consideration for self-assessment since they would typically be under the care of a physician and therefore a CHD risk-reduction strategy should already be in place.

In the context of self-directed care, it seemed reasonable to focus on the factors in Table 1 that the individual can self-identify as the major basis for risk assessment. Additionally, there are important life-style risk factors such as being overweight (determined by measuring Body Mass Index - BMI), truncal obesity (determined simply by waist measurement) and physical inactivity that can be assessed easily and that, when present, worsen CHD risk. Including these in risk-modelling would have the additional benefit that attention is directed from the outset to some important modifiable lifestyle components of risk.

Assigning broad categories of risk is possible using the starting point of age and sex and then looking at the impact of adding one or more additional self-determined risk factors.
Population lifetime risks for CHD are greatest for men aged 45 years or more and women aged 55 years or more. If we take those age thresholds as the starting point, and in the absence of measurements we assume population average levels of TC:HDL of 5.3 for men and 4.6 for women\textsuperscript{12}, we can see the impact of adding additional risk factors (using the Joint British Guidelines charts of the time)\textsuperscript{5}:

Family history of early CHD in first-degree relatives increases CHD risk by approximately 1.5 fold. This would give absolute 10 year risk values of at least 10% for the age ranges given, across the ranges of likely systolic blood pressures.

Smoking (i.e. current smoker or smoker within the previous 5 year) raises ten year CHD risk well into the 10-15% range for this population.

Obesity alone, but especially if accompanied by truncal obesity, is associated with poor outcomes for CHD disease and increases the risk of dyslipidaemias, insulin intolerance and hypertension. The presence of a BMI above 25kg/sqm (WHO definition of overweight) or a waist measurement of 102cm (40 ins) for men or 88cm (35 ins) for women (truncal or central obesity)\textsuperscript{14} would also identify a moderate-risk population. Although formal assessment of the impact of obesity on 10 year CHD risk had not been included in the 1998 Joint British Guidelines, it was considered likely that the presence of this factor would boost baseline 10 year risk in this age population well into the moderate (10 – 15%) category\textsuperscript{15}. To illustrate this, it was estimated from cohort studies that a 1 unit change in BMI (equivalent in a man of average height to a 3kg loss of body weight) reduced risk of CHD by 10%\textsuperscript{16}.

Sedentary lifestyle is a well-established underlying risk factor for CHD\textsuperscript{16}. Conversely, regular exercise improves lipid profiles (e.g. by raising HDL cholesterol), and has beneficial effects on blood pressure and cardiovascular function. Although it is difficult to calculate the effect of a sedentary lifestyle on absolute CHD risk, the panel believed it should ideally be part of the original assessment and in borderline cases it should favour intervention.

Thus a pragmatic approach to identifying those at moderate risk was to apply a threshold for age according to sex (45 years and above for men and 55 years and above for women) and select those in that population with one or more of the following risk factors as eligible for self-treatment:

Family history of premature CHD (<55years in men and <65years in women) in a first-degree relative.

Smoker: either current or in the previous 5 years.

Overweight: Body Mass Index >25 kg/sqm or truncal obesity (waist: 102cm or 40 ins in men; 88cm or 35 ins in women).

A sedentary lifestyle (defined as no formal exercise and a non-manual job) would favour treatment in borderline cases.
This assessment of risk relied on the Joint British Guidelines, which in turn were based on the calculations in the Framingham model. Some had reported that applying the Framingham model to a UK population cohort underestimated the CHD risk at lower levels of absolute risk. Therefore it was likely that these estimates of risk were conservative. Also, these absolute risk levels are for non-fatal myocardial infarction and CHD deaths alone; if we were to include other CHD disease endpoints (such as unstable angina) the risk in this population of developing CHD disease would be substantially higher.

INTERVENTIONS FOR SELF-CARE IN PREVENTION OF CHD RISK:

General Principle

The panel felt that once an individual was identified as being at moderate risk of CHD, the aim should be to reduce that risk by all means. Smoking cessation is clearly the priority for smokers and pharmacists were well placed to supervise the established programs. Dietary advice should also be given to all to enable healthier food choices, but particular attention to sensible weight loss diets should be encouraged in those that are overweight and in those with truncal obesity. Likewise advice on increasing aerobic exercise is appropriate to all people at moderate risk but particularly to those that have a sedentary lifestyle.

Reduction of LDL-C cholesterol using statins reduces risk regardless of the starting value. It was the panel’s view that this intervention should be given at the same time as lifestyle interventions, because LDL-C reduction with statins will produce benefit whatever else the at-risk person does. If, as is frequently the case, people take time to improve lifestyle habits, it did not seem sensible to deny them the benefit of a statin in the interim. However statin treatment should clearly be only one part of a comprehensive program of education, advice and ongoing encouragement across the range of interventions.

Choosing a dose of statin and likely benefit

Many large, long-term, randomised controlled clinical studies including populations at a variety of levels of CHD risk, were published prior to 2004 and confirmed that lowering LDL-C with statins reduces CHD mortality and morbidity. A meta-analysis of some of these studies showed that statin treatment producing approximately a 30% reduction in LDL-C produced a 30% decline in major coronary events both in populations that initially had high cholesterol levels and in those where initial levels were lower, regardless of sex or age.

Table 2 is extracted from a meta-analysis of statin dosage and LDL-C reduction from 164 short-term studies with statins. Absolute reductions with 10 and 20 mg of simvastatin in this analysis (standardised to the mean starting serum LDL-C in these studies of 4.8mmol/l) were 1.31mmol/l and 1.54mmol/l respectively, reflecting relative reductions of 27% and 32% for the 2 doses. Relative potencies of some other statins used in the major endpoint studies are also included in this table.
On this basis, a 1.3mmol absolute reduction in LDL-C might be expected to produce at least a 30% reduction in CHD risk. This may be conservative since it is recognised that estimates of risk reduction based on meta-analysis of endpoint studies lag behind the benefit for the same LDL-C difference in observational studies²⁵.

Simvastatin 10mg seemed a reasonable choice of dose on the basis of the likely effect in the target population and was in accord with the dose of Lovastatin (20mg) under discussion for self-medication in the US. This in turn was driven by the AirForce/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TEXCAPS) data, which represented the best outcome study in a ‘low to moderate’ CHD risk population (see below).

Statins are very well tolerated drugs, but rare adverse events such as myositis show a clear dose-relationship and may also occur in interaction settings when statin levels are boosted. For these reasons also, a choice of dose at the lower end of the range of effective doses seemed prudent for the pharmacy setting.

**The process of approval**

The ‘P’ application for simvastatin 10mg was submitted in late summer 2003. Initial assessment by the MHRA went smoothly, not least because the agency had been closely involved with the evolution of the application before submission, and so there were no surprises.

The body of experts advising the UK government on medicines licensing at the time was the Committee on Safety of Medicines (CSM). This body invited a special panel of advisers including epidemiologists and cardiovascular specialists to give their views on the application. They also took the unprecedented step of inviting the sponsor company and its advisers to an oral hearing, where the rationale for the switch was presented and discussed.

The CSM left the proposed means of selecting suitable patients for Zocor Heart Pro relatively unchanged – except to simplify it somewhat by specifying that men over the age of 55 years would be in the moderate (10-15% risk of CHD) risk category without additional risk factors.

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### Table 2: Absolute reductions* mmol/l (with 95%CI) and percentage reductions# in serum LDL-C. Summary estimates from 164 randomised placebo-controlled trials.  

<table>
<thead>
<tr>
<th>Statin</th>
<th>5mg</th>
<th>10mg</th>
<th>20mg</th>
<th>40mg</th>
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</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>-</td>
<td>1.02 (0.71 -1.34)</td>
<td>1.4 (1.21 to 1.59)</td>
<td>1.77 (1.6 to 1.94)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>0.73 (0.54 to 0.92)</td>
<td>0.95 (0.83 to 1.07)</td>
<td>1.17 (1.10 to 1.23)</td>
<td>1.38 (1.31 to 1.46)</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>1.08 (0.93 to 1.22)</td>
<td>1.31 (1.22 to 1.40)</td>
<td>1.54 (1.46 to 1.63)</td>
<td>1.78 (1.66 to 1.90)</td>
</tr>
</tbody>
</table>

*standardised to mean concentration of LDL-C before treatment (4.8mmol/l)  
# percentage reductions are independent of pre-treatment LDL-C
They also suggested that ethnicity (South Asian ethnic origin i.e. from the Indian subcontinent that includes India, Bangladesh, Pakistan or Sri Lanka), should be added as a qualifying risk factor added to age and sex, since this increased CHD risk by a factor of approximately 1.45.

The committee was concerned that pharmacists should be able to select consumers as suitable or unsuitable for simavastatin and asked the company to test the pharmacy materials (which comprised a self-administered consumer questionnaire and pharmacist checklist). Testing of prototype materials in pharmacy26 confirmed that these ‘tools’ functioned well in selecting appropriate consumers.

Two other aspects of the model approved for consultation27 were noteworthy: a) the removal of the requirement for liver function testing before starting treatment (on the basis that this requirement was not evidence-based in people without liver disease), and b) the lack of a requirement for cholesterol testing before or after treatment initiation. The section of the consultation document relevant to cholesterol testing was:

Provided compliance is adequate, most people at moderate risk should achieve reductions in LDL-C of around 27% with 10mg of simvastatin daily. If the individual has a moderate risk of CHD, reducing their level of cholesterol will reduce their risk. For this reason it is not essential for them to know the level of cholesterol in their blood. There is no specific requirement to either identify their LDL-C level before treatment or to monitor this afterwards. However, the consumer will be offered the opportunity to test their cholesterol levels and to receive follow up advice from their pharmacist.

This was a radical departure from clinical practice at the time which still used measurement of cholesterol status as a core part of CHD risk assessment, albeit for high risk patients.

The consultation produced an extraordinary 100 responses (available on the MHRA website), split evenly: one third of responses were in favour, one third were opposed and one third were not opposed but raised issues27. The CSM judged that none of the issues raised in consultation were new (i.e. had not already been considered before consultation), and so the approval was granted.

**Reaction to the launch**

Coverage of the Zocor Heart Pro launch was unprecedented, producing extensive comment in national and international news media. From the outset there were many voices raised against the switch in the UK. Spokespersons for UK general practice organisations (principally the Royal College of General Practitioners) were prominent in criticising the move. This was debatably the critical factor in influencing the attitude of pharmacists who were thrust into the spotlight as the new purveyors of an important class of drugs for the prevention of a serious illness; but apparently in the face of opposition from their local doctors.
The most repeated criticisms of the switch are discussed below, with rationalization for the relevant elements of the ZHP switch ‘model’.

‘There are no data to support the use of this dose of simvastatin in this population’.

The risk-reduction available with lowering LDL-C had been established in low\textsuperscript{18}, moderate\textsuperscript{19} and high-risk\textsuperscript{4} populations. It is particularly relevant to look at the principal primary prevention studies West of Scotland Coronary Prevention Study (WOSCOP)\textsuperscript{19} and AFCAPS/TexCAPS,\textsuperscript{18} with placebo event rates corresponding to a 10-year population risk of 16% and 6% respectively (Table 3).

<table>
<thead>
<tr>
<th>Table 3: Primary Prevention Studies with Statins Compared</th>
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<tbody>
<tr>
<td><strong>Subjects</strong> (% male)</td>
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<tr>
<td>----------------------</td>
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<tr>
<td>Subjects</td>
</tr>
<tr>
<td>Average age (range) years</td>
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<tr>
<td>Previous CHD (%)</td>
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<tr>
<td>Active treatment (mg/day)</td>
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<tr>
<td>Baseline TC (mmol/l) (HDL&lt;1.2)</td>
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<tr>
<td>Average TC reduction (mmol/l)</td>
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<tr>
<td>Average LDL-C reduction (%)</td>
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<tr>
<td>Placebo event rate (%) *</td>
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<tr>
<td>Statin event rate (%) *</td>
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<tr>
<td>Relative risk reduction (95% CI)</td>
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* based on primary endpoint: AFCAPS/TexCAPS - fatal and non fatal MI, unstable angina or sudden cardiac death; WOSCOPS - definite CHD death or non fatal MI. †Event rate in 5 years.

The populations in these studies ‘bracket’ the range of risk (10-15% 10 year risk of a major coronary event) proposed for self-care. The mean level of LDL-C reduction in these studies was 26% and 25% respectively, close to the mean of 27% observed in studies with simvastatin 10mg\textsuperscript{25}. It seemed reasonable to expect a similar response to a similar degree of LDL-C reduction in this similar moderate risk self care population.

The ‘cholesterol hypothesis’ in relation to coronary heart disease has been the subject of more and larger endpoint studies than any other question in modern medicine. It seemed illusory to suggest that yet another (presumably placebo-controlled) endpoint study in the specific
population proposed for self-care would add anything to our knowledge about the relationship between lowering LDL-C and lowering risk. Were such a study to be proposed, it is debatable whether it could have been undertaken on ethical grounds, given the state of knowledge at the time.

‘10mg of simvastatin is too low to produce a meaningful benefit’

When statins were first introduced it was common to prescribe what would now be regarded as ‘low’ doses and titrate upwards. Until the early 2000’s 10mg of simvastatin was one of the most prescribed doses by doctors in the UK and in 2003 it still accounted for approximately 20% of prescriptions (personal communication MSD to S.G. Mann 2003). The reasons for this were partly historical and partly pharmacological.

In the early years of a new drug class it is typical that doctors use the lowest possible dose to achieve the desired effect. Many patients would have achieved satisfactory cholesterol reduction on these doses (particularly given the more relaxed targets of the time) and therefore have needed no further titration. Pharmacologically, simvastatin exhibits a log-linear dose response relationship: so doubling the dose from 10mg to 20mg will increase LDL-C reduction from 27% to 32%; doubling it again to 40mg will add a further 5% incremental lowering.

The early 2000’s saw a step-change in the way UK doctors prescribed statins, and initiation of treatment on higher doses became commonplace. One important factor in this was the use of higher doses in endpoint studies such as the 4S study and the Medical Research Council/British Heart Foundation funded Heart Protection Study performed in high risk populations. In these studies the benefit of reducing LDL-C in reducing CHD events was established beyond doubt and the safety profile of simvastatin at 40mg was demonstrated emphatically. Together with the accumulated evidence of many years marketed use testifying to the excellent tolerability of the drug, the logic to maximise benefit in those at most risk of CHD events by starting with 40mg was compelling. In these patients it is sound practice to lower cholesterol aggressively and keep it as low as possible to reduce their risk. The role of statins is especially important in this group since their ability to modify their accumulated risk by lifestyle modifications may be limited.

It is questionable whether the same approach is justifiable for people at lower risk. The main driver for CHD risk is age, so typically moderate risk populations will be younger and/or fitter than high-risk populations. These people, particularly the younger ones whose risk is partially driven by lifestyle factors, have more opportunity to lower their accumulated lifetime risk by non-pharmacological interventions. Reducing LDL-C in those at moderate risk (10 – 15% 10 year risk of a major coronary event) may be the single most important part of a risk-reduction strategy, but it should be accompanied by lifestyle improvement.

LESSONS LEARNED FROM THE SIMVASTATIN SWITCH

Six years after the launch of simvastatin in the UK it is clear that the switch has failed to
deliver the benefit to public health that many hoped for. The reasons for this are complex and include commercial factors outside the scope of this analysis. However, with the perspective of time and the accumulated experience of subsequent switches, some broad conclusions can be drawn:

1. If what is proposed in the switch diverges too much from what primary care doctors are being told to do at the time, then this will generate misunderstanding and criticism. This in turn can lead to:
   a. Consumer confusion with doctors appearing to criticise what pharmacists are being asked to do.
   b. Pharmacist anxiety that they are out of step with accepted medical practice.

Zocor Heart Pro was aimed at primary prevention in a population at much lower risk than GPs were able to target with statins in the NHS at the time. Subsequently guidelines changed and allowed statin prescribing in individuals at 20% CVD risk (equivalent to 15% 10 year risk of a CHD event), a population adjacent in risk to the proposed self care population. However for the critical time around launch, GP guidelines diverged from the evolving expert opinion that statins should be available for primary prevention at lower levels of risk.

Similarly, cholesterol testing was an accepted part of CHD risk assessment in primary care at the time and a level of total cholesterol concentration $\geq 5.0$mmol/l was required to qualify for NHS statin treatment.

The ZHP model did not rely on knowing cholesterol status before treatment, reflecting strong evidence that benefit did not rely on starting cholesterol levels. However, the use of a drug to lower cholesterol in the absence of cholesterol testing proved counterintuitive for doctors and pharmacists, and if consumers did not know their cholesterol level, they were often not sold the drug.

2. The dose proposed for a switch should not be in conflict with the dose primary care doctors are being told to use at the same time (and therefore the dose pharmacist are familiar with dispensing). There may be good reasons for choosing a different dose for the OTC population, but any discrepancy will still be a major problem.

There was a sound rationale for using 10mg of simvastatin for the moderate risk population targeted for self-medication, since this dose would produce around 74% of the LDL-C lowering available with 40mg (due to the log-linear nature of the dose response for statins) while reducing the risk of rare dose-related adverse events, particularly in drug interaction settings that raise statin levels.

Nonetheless, the use of this dose was criticised because it had not been studied in the specific self-medication population. To do such a study while ignoring the mass of data from which likely benefit could be deduced would have been ethically questionable.
3. A ‘first in class’ switch will always come under particular scrutiny. This can lead to important consequences: e.g. the supply model may be over-complicated in an attempt to make it as ‘safe’ as possible. This can make pharmacy delivery of a switch problematic.

The ZHP switch was one of the first to employ, at the request of the regulatory authorities, a validated consumer questionnaire and pharmacist guidance algorithm. Although these materials were designed to be easy to use and the patient selection criteria were relatively simple, the perception in pharmacies was that this was a complex model compared to what had gone before. Subsequent switches (e.g. sumatriptan in the UK) that have required the use of a questionnaire have also faced problems of acceptance into routine pharmacy practice.

4. If consumer knowledge in a particular area is low (as with the UK population and cardiovascular risk), then the task of education cannot be undertaken by a company launching a new product alone. Unless all relevant ‘stakeholders’ e.g. doctors, pharmacists, government, charities, are demonstrably united in recommending a particular course of action, then changing consumer behaviour is an unrealistic expectation.

Cardiovascular risk and the role of interventions to reduce it on a population basis are complex issues and require long term communication of a consistent message to change behaviours. The introduction of a pharmacological intervention to reduce CHD risk in specific populations produced mixed messages from the various stakeholder groups. Some expressed concern that people might abandon attempts to adopt healthy lifestyles in favour of a ‘quick fix’ daily tablet. In fact the ZHP launch was unique in offering a comprehensive package of measures to reduce CHD risk, with advice tailored to the particular lifestyle issues of the individual. Prospective studies were planned to evaluate to what extent people taking ZHP also adopted healthy lifestyles; however poor take-up of the drug rendered such studies impossible.

CONCLUSION

Cardiovascular disease is the single leading cause of death for adults worldwide. Although deaths from CVD have fallen substantially in recent decades, it will remain the major cause of death and disability in Western populations well into this century. Self care should play a role in tackling health problems that are simply too big to be managed entirely within doctor-led healthcare systems. CVD is a largely preventable condition, but early pharmacological intervention in moderate risk populations would be hugely expensive if introduced on a population basis.

The switch of ZHP in the UK was a bold attempt to bring primary prevention of CHD into the reach of a large population, which, available evidence suggested, could benefit substantially. These were individuals who would not receive a statin under a financially constrained healthcare system.

This analysis suggests that some of the thinking which underpinned the UK simvastatin switch
may have diverged too far from mainstream primary care practice at the time, particularly since guidelines were in the process of revision. Future switches aimed at primary prevention will face similar problems unless all potential stakeholders can be convinced to recommend a cohesive strategy, with self-medication having an agreed place.

It would be wrong to assume that the story of non-prescription statins necessarily ends here. In a recent Editorial in Nature Reviews Cardiology\(^2\), Fuster comments: ‘...the reality is that non-prescription statins are already available in the UK and are likely to become available in other countries at some point in the near future. Furthermore, non-pharmaceutical supplements that act to decrease LDL-cholesterol levels are easily accessible worldwide. The current debate, therefore, should not center on whether we should allow non-prescription statins, but instead focus on how we should educate people on the use of lipid-lowering therapies.’

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Conflict of Interest Statement: The author was an employee of Johnson & Johnson MSD and McNeil Europe from 1993 until 2005. He was the clinical leader on the simvastatin 10mg switch project for the company.

REFERENCES


