

Over-the-counter simvastatin — is it hype or a genuine hope for the future?

Simvastatin 10mg will soon be available as an over-the-counter medicine in pharmacies. **Magnus Hird** examines the evidence for the drug's use and provides useful tips information for pharmacists who will be selling the medicine

The Medicines and Healthcare products Regulatory Authority (MHRA) recently announced that approval had been given to reclassify 10mg simvastatin as an over-the-counter medicine.

It has been licensed for sale to patients at moderate risk of heart disease to reduce their risk of a first major coronary event, eg, a non-fatal myocardial infarction or death due to coronary heart disease.¹

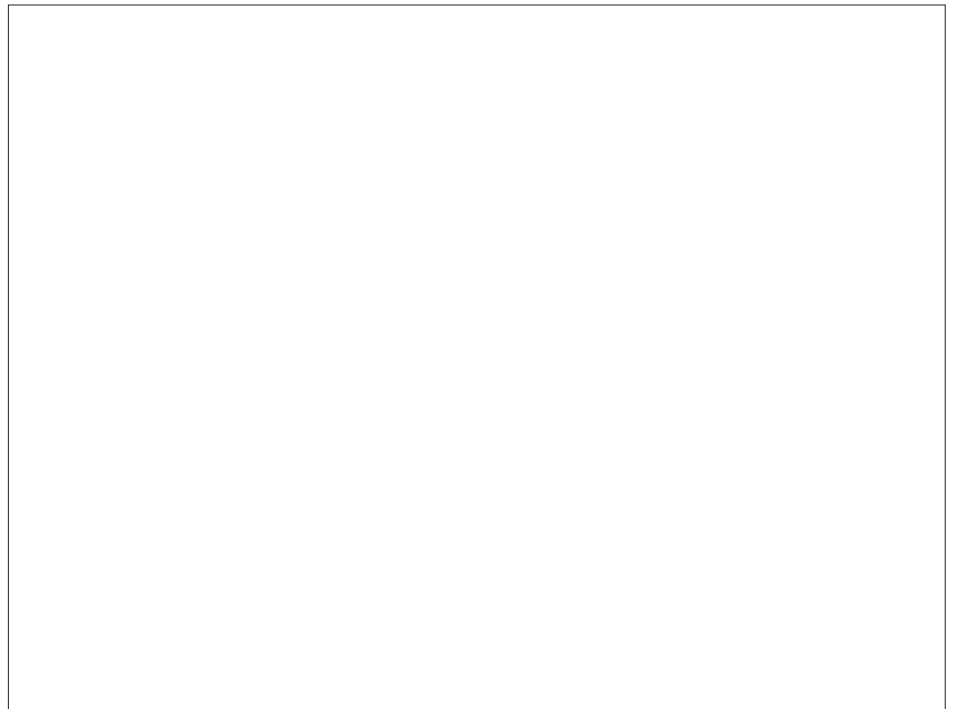
The consultation process drew many comments, some supportive and some in opposition to the switch. Since the announcement the British Medical Association,² *The Lancet*,³ the King's Fund² and the Consumers' Association^{2,4} have levelled criticisms at the decision.

Some of these relate to political policy, citing the change as evidence of a two-tier NHS and asking why, if wider availability would be beneficial, the Government is not funding it. However, alongside the politics lie a number of serious concerns relating to the clinical merits of the reclassification:

- There have been no clinical trials of this dose of simvastatin
- There have been no clinical trials in an OTC population
- There are no data relating to compliance with OTC simvastatin
- It is not known whether pharmacists will be able to assess an individual's risk of CHD appropriately
- It is not known whether the availability of OTC simvastatin may, in fact, reduce healthy lifestyle changes
- The risks of treatment, and whether pharmacists will be vigilant for them, are unknown
- The benefits have not been quantified so patients cannot make an informed choice

Few sources have attempted to examine the information available and establish how these concerns might be allayed.

This article attempts to do that and to help inform pharmacists who may be dealing with over-the-counter simvastatin. It should be read alongside the Royal Pharmaceutical Society's practice guidance, and the medi-



How patients will be identified for OTC treatment is based on the presence or absence of a number of risk factors, primarily age, smoking status, ethnicity, overweight/obesity and premature family history

cine's summary of product characteristics and other information from the manufacturer.

Pharmacists should also consider what other issues this article raises for them and how they might satisfy these continuing professional development needs.

A two-tier system?

The NHS currently offers lipid-lowering treatment to patients who have already had an event (secondary prevention) and those at high-risk of a first event (primary prevention). The threshold for primary prevention treatment is currently 30 per cent risk over 10 years, with a consensus to roll this back to 15 per cent once resources allow, but further information is awaited from the National Institute for Clinical Excellence in 2005. The decision is purely one of cost-effectiveness: as the risk of an event falls we have to treat more and more individuals in order to prevent one occurring.

Therefore the cost per event avoided rises until it reaches a point where it represents a less appropriate use of public funds than many other competing health care priorities which, if funded with the same money, would

produce greater health benefits for the population. The alternative would be to increase the NHS budget, either by raising taxes or by spending less on other things such as education, transport or foreign aid, both methods that are unlikely to be popular with the public. Yet for individuals who may place a higher value on avoiding a heart attack than the NHS, treatment, despite their low level of risk, may be something they desire and they may be willing to pay for it.

This simply reflects the essential nature of a publicly funded health system: it will never be possible to provide every existing intervention that could be of benefit to every single patient.

What about an OTC population?

The target group for OTC simvastatin is men and women at moderate risk of a first major CHD event, ie, primary prevention. In numerical terms it is aimed at people who have an approximate risk of such an event between 10 per cent and 15 per cent over the next 10 years, ie, the group immediately below the threshold at which the NHS intends to provide treatment.

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What we must remember is that the 15 per cent threshold is not set because treatment does not work below this level, but because it is not cost-effective for the public purse. There are a number of trials that have studied the effects of treatment in moderate risk primary prevention groups. These are summarised in Table 1, from which it can be clearly seen that there is a published evidence base involving over 23,000 patients between roughly 6 per cent and 16 per cent risk over 10 years.

This establishes that the target OTC population will be at similar levels of risk as those already studied in clinical trials. Yet OTC patients and trial participants are not necessarily the same. Trials tend to select motivated and informed patients who have relatively uncomplicated disease (or medical histories). They also involve regular and detailed assessments which, in themselves, seem to improve health outcomes. (One only has to look at placebo response rates to see this.) So, the question for us is how different might this be from an OTC group?

Patients buying a medicine over the counter to take long term must be well motivated by definition. Regular daily use for many years will be necessary to obtain benefits in terms of a reduced risk of coronary events. If they were not well motivated then we would not expect them to commit to the regular trips to a pharmacy to purchase the product, never mind the financial outlay. These regular trips may also mimic some of the effects of the assessment visits in trials, but only as long as pharmacists and their staff take the time to check progress, reinforce healthy lifestyle advice and provide an opportunity for questions. The proposed OTC target group is also a relatively uncomplicated set of patients: those with serious co-morbidities are not suitable for treatment.

In addition, the way patients will be identified for OTC treatment is based on the presence or absence of a number of risk factors, primarily age, smoking status, ethnicity, overweight/obesity and premature family history. These characteristics are similar to those used in the trials highlighted in Table 1 (middle-aged and older patients with a number of risk factors, of which raised cholesterol is not necessarily one). So perhaps on reflection our OTC patients will not be that dissimilar from those in clinical trials.

In terms of compliance, it may not be unreasonable to expect relatively high levels in an OTC population, at least in those who want to benefit. Compliance with prescribed medicines often suffers because the patient does not understand the reason for treatment or disagrees with the prescriber's views. In the OTC scenario the patient seeking out treatment and the "prescriber" become the same individual so it is difficult to see how these conflicts could arise and therefore their negative impact on compliance is avoided.

It is known that compliance with prescribed statins is poor: recent research has shown that in a group of elderly primary pre-

Table 1: Trials that have studied the effects of treatment in moderate risk primary prevention groups

| Trial | Study details | Level of risk* |
|-----------------------------|--|---|
| WOSCOPS ⁵ | 6,595 Scottish males (aged 45–64) with no history of MI and LDL between 4 and 6mmol/L despite dietary advice. Treated with pravastatin 40mg daily. Main outcome was combination of non-fatal MI and CHD death. | 7.9% over 4.9 years or 16.1% over 10 years† |
| AFCAPS/TexCAPS ⁶ | 6,605 American men (aged 45–73) and post menopausal women (55–73) with normal cholesterol and LDL but low HDL (a coronary risk factor) and no history of CHD or vascular events, diabetes or significant obesity. Treated with lovastatin 20–40mg daily. Main outcome was combination of fatal or non-fatal MI, unstable angina or sudden cardiac death. However, subtraction of unstable angina cases is possible as they were reported separately. This allows us to use the same outcome as other trials. | 2.9% over 5.2 years or 5.6% over 10 years† |
| ASCOT-LLA ⁷ | 10,305 hypertensive European men and women (40–79) with total cholesterol less than 6.5mmol/L and at least three other CHD risk factors (but no existing CHD). Treated with atorvastatin 10mg daily. Main outcome was combination of non-fatal MI and fatal CHD. | 3.0% over 3.3 years or 9.1% over 10 years† |

*Percentage of patients in the placebo group that had a non-fatal MI or died from CHD over the period of the trial
†Assuming that the risk rate remains linear over the longer period

Table 2: Trial outcomes

| Trial | Outcomes (placebo v active treatment) | RRR | NNT |
|-------------------------------|--|-----|-----|
| WOSCOPS (4.9 years) | ■ Non-fatal MI or fatal CHD: 7.9% v 5.5% ($P < 0.001$) | 30% | 42 |
| | ■ Non-fatal MI: 6.5% v 4.6% ($P < 0.001$) | 29% | 53 |
| | ■ Fatal or non-fatal stroke: 1.6% v 1.6% ($P = NS$) | | |
| | ■ All cardiovascular death: 2.3% v 1.6% ($P = 0.033$) | 30% | 143 |
| | ■ All cause mortality: 4.1% v 3.2% ($P = NS$) | | |
| AFCAPS/TexCAPS (5.2 years) | ■ Fatal or non-fatal MI or sudden cardiac death: 2.91% v 1.69% | 42% | 82 |
| | ■ Non-fatal MI not reported separately | | |
| | ■ Stroke not reported separately | | |
| | ■ Fatal cardiovascular events: 0.76% v 0.51% ($P = NS$) | | |
| | ■ All cause mortality not reported | | |
| ASCOT-LLA (3.3 years) | ■ Non-fatal MI or fatal CHD: 3.0% v 1.9% ($P = 0.0005$) | 37% | 91 |
| | ■ Non-fatal MI not reported separately | | |
| | ■ Fatal and non-fatal stroke: 2.4% v 1.7% ($P = 0.0236$) | 29% | 143 |
| | ■ Cardiovascular mortality: 1.6% v 1.4% ($P = NS$) | | |
| | ■ All cause mortality: 4.1% v 3.6% ($P = NS$) | | |

RRR = relative risk reduction, NNT = number needed to treat, NS = not significant

vention patients only one in four were still taking the statin after two years⁸ In the Heart Protection Study, conducted in a group of very high risk secondary prevention patients, compliance (meaning patients taking at least 80 per cent of their doses) was 85 per cent.⁹ Despite this, treatment in the trials was beneficial and we continue to prescribe statins (and expect benefit) even though they are poorly adhered to. Reflecting on these figures it becomes apparent that compliance with OTC simvastatin is unlikely to be worse than other real-life situations and may even approach the high levels seen in clinical trials.

In summary, given all these similarities, rather than differences, it seems possible that an OTC population would stand to benefit in similar proportional ways as a trial population, or at least a real-life population. So these criticisms of the OTC decision perhaps appear unfounded.

Will it work?

It is correct to assert that there have been no clinical trials of 10mg simvastatin (apart from the two patients in 4S trial who took it, and they were secondary prevention¹⁰). However when one examines the literature it emerges that there has only been one trial of simvastatin at any strength for primary prevention (and that was a subgroup of the whole trial). Even here the vast majority of the primary prevention group had complicated disease (eg, diabetes, stroke or transient ischaemic attack, or peripheral vascular disease). Despite the fact that this trial was only published in 2002, simvastatin has been advocated for use in primary prevention for much longer. In addition recommendations made do not differentiate these complicated patients from the less complicated ones who have not been studied. So if we feel it necessary to question the evidence for simvas-

Table 3: The CURVES study summarised

| Drug | Reduction in LDL cholesterol at dose of: | | | |
|--------------|--|------|------|------|
| | 10mg | 20mg | 40mg | 80mg |
| Atorvastatin | 38% | 46% | 51% | 54% |
| Fluvastatin | NS | 17% | 23% | NS |
| Lovastatin | NS | 29% | 31% | 48% |
| Pravastatin | 19% | 24% | 34% | NS |
| Simvastatin | 28% | 35% | 41% | NS |

NS= not studied

tatin 10mg perhaps we should equally question the basis for these recommendations.

A fact of life is that we often do not have the direct evidence we would like for the interventions we make: there will never be a robust clinical trial to give us an unquestionable answer for everything we do. In reality we are forced to examine the evidence we do have and make judgements about how it would apply in different circumstances. This process is what lies behind the recommendations above; we must also apply similar logic in the case of simvastatin 10mg to make our judgement.

The three primary prevention trials all used different drugs and at varying doses, but in all trials there were significant benefits (see Table 2). These benefits appear to be reductions in non-fatal myocardial infarction and possibly strokes and deaths due to cardiovascular causes. Lipid-lowering treatment in primary prevention populations has not been shown to reduce overall mortality, but it perhaps allows life to be lived in better health.^{11,12} However, at least one review suggests that over a longer period these benefits may become significant (the all-cause mortality result was of borderline significance in WOSCOPS: $P=0.051$).¹² At the end of the day overall mortality is not the only worthwhile outcome: non-fatal myocardial infarction and stroke still have huge implications for patients. Our question is whether simvastatin 10mg would achieve similar outcomes to the trial treatments.

The consensus of opinion is that the magnitude of relative benefit is related to the reduction in cholesterol, particularly low-density lipoprotein cholesterol, but not the baseline or final value. This view is reiterated in *Clinical Evidence*.¹¹ In the "primary prevention" section the authors state that "absolute benefit is related to an individual's baseline risk of cardiovascular events and to the degree of cholesterol lowering". The authors of the Heart Protection Study state that "lowering LDL cholesterol with a statin produces a substantial reduction in the incidence of major vascular events"⁹ and all the major guidelines on prevention and treatment of coronary heart disease urge us to lower cholesterol.

So perhaps the answer to our question lies in examining the lipid-lowering effects of 10mg simvastatin in comparison with that of the other proven primary prevention treatments. Table 3 summarises the results of the

Table 4: Objective estimate of the value of treatment

| Patients estimated 10-year absolute CHD risk (the boundaries of the OTC group) | Apply 24% reduction | Approximate Number Needed to Treat to avoid 1 CHD event* over: | |
|--|---------------------|--|---------|
| | | 10 years | 5 years |
| 10% | 7.6% | 42 | 84 |
| 15% | 11.4% | 28 | 56 |
| 12.5%† | 9.5% | 33 | 66 |

*A non-fatal myocardial infarction or death due to coronary heart disease

†Mean value, because the actual risk is not known

CURVES study, a short-term randomised open trial to examine the effects of several drugs and doses on cholesterol levels in a middle-aged (mean age 55 years) mainly primary prevention (83 per cent) population.¹³

Simvastatin 10mg appears to lower LDL cholesterol by 28 per cent. (This is supported by information in the SPC for Zocor which states an approximate 30 per cent reduction.) Pravastatin 40mg (as used in WOSCOPS) lowers LDL cholesterol by 34 per cent, lovastatin 20–40mg (as used in AFCAPS/TexCAPS) by 29–31 per cent and atorvastatin 10mg (as used in ASCOT-LLA) by 38 per cent.

In the actual clinical trials over longer periods the LDL reductions achieved were 26 per cent (WOSCOPS), 25 per cent (AFCAPS/TexCAPS) and 32 per cent (ASCOT-LLA). In other words on average about 80 per cent of the size of the short-term results from CURVES. If we apply this logic to the simvastatin 10mg results, we may expect an LDL reduction of about 23 per cent in a trial-like situation, which, as discussed above, could be similar to a real-life, long-term use OTC population.

Our confidence in simvastatin 10mg should be bolstered by evidence that as a drug it does confer benefits: we are not trying to extrapolate cholesterol-lowering capacity in a compound not proven to reduce the rate of cardiovascular events.

In summary, given these effects it would appear highly likely that simvastatin 10mg will be effective as a treatment.

What will the benefits be?

Simply telling a patient that a treatment will be "beneficial" will often not be sufficient to engender a concordant decision. Rightly so, more and more patients want to know what the benefit may be, how that applies to them and what the potential harms are that they risk in the process. Pharmacists should be at the forefront of putting this approach to treatment decisions into practice. However, this stage is where extrapolation of the evidence starts to become much more difficult. Without clinical trials we can only make informed estimates and we should be honest with patients about this. Critically though, the same is true of many accepted interventions and other aspects of health care.

A meta-analysis of lipid-lowering treatment in primary prevention by Pignone *et*

al concluded that "treatment will reduce the relative risk of coronary heart disease events and coronary heart disease mortality by about 30 per cent, independent of absolute risk".¹² This is further supported by many other trials, which show a remarkably consistent effect: that statin treatment confers a reduction in the risk of events whichever group you treat, whether they are primary or secondary prevention, younger or older, male or female, with or without a number of different co-morbidities and so on. Pignone *et al* go on to say that "the absolute risk reduction from treatment, therefore, is proportional to the underlying risk in the person or populations being considered for treatment" but reinforce that benefits accrue over "five to seven years" and that there is no proven effect on all-cause mortality. This meta-analysis was based on a number of statin studies across which the LDL-lowering effect was 25–32 per cent. Our estimate above is that OTC use of simvastatin 10mg would lower LDL by about 23 per cent — in other words, about 80 per cent of the average effect seen in the trials, which we have already established are probably quite similar to a motivated OTC group.

Given that the consensus of opinion accepts that the relative benefits are proportional to LDL reduction, we could apply this 80 per cent adjustment to the 30 per cent relative risk reduction figure proposed by Pignone *et al*. This would lead us to believe that simvastatin 10mg used OTC may reduce the relative risk of CHD events and CHD mortality by 24 per cent.

The only thing that remains is to apply this relative risk reduction to the absolute risk levels that the target OTC patients will be at. This allows us to provide a best-guess, objective estimate of the value of treatment, shown in Table 4. It is worth remembering that these figures could vary one way or the other quite significantly; they are only estimates based on a logical extension of the published literature. However an appraisal by the University of British Columbia estimated similar values.³

What are the risks?

Statins are generally well-tolerated medicines. The SPC for Zocor¹⁴ states that about one patient in 50 in clinical trials withdrew due to adverse effects. In the Heart Protection Study 4.9 per cent of the simvastatin group stopped taking the study medicine over five years, but

Panel 1: How to communicate information about the benefits of treatment to patients

A: Relative risk reduction

"Taking this treatment in the long-term, eg, for five to 10 years, will probably reduce your chance of having a heart attack or dying from CHD by about a quarter; you will still be at risk, just slightly less so."

B: Number needed to treat

"If 66 people like you take this treatment for five years one of you will probably avoid having a heart attack or dying from CHD that would have done if they had not been taking the treatment. Some of the 66 will still have heart attacks or die."

C: Population effects

"If we take 1,000 people like you, then without treatment over five years, 63 will have a heart attack or die from CHD and 937 will not.

"If all 1,000 took this treatment for five years, 48 will have a heart attack or die and 952 will not.

"In other words we probably avoid 15 events in these 1,000 people over five years. You could be one of the 15 (benefit from treatment), but you could also be one of the 48 (have an event with or without treatment) or one of the 937 (do not have an event with or without treatment)."

Panel 2: How to communicate information about the risks of treatment to patients

A: Number needed to harm

"In trials one person in every 20 stopped taking the treatment, however this happened just as often with the placebo as the active drug: they were both well tolerated"

"For every 500 people that take this medicine for five years one person will have to stop taking it due to problems with their liver. For every 1,667 people, one will develop potentially serious muscle problems."

B: Population effects

"If we take 1,000 people, then without treatment over five years 50 would stop taking a medicine if they had been taking one (eg, a placebo). Three people will have to stop taking the medicine due to persistent liver disturbance and there is a 50/50 chance that one person will have potentially serious muscle problems; 946 or 947 people would have no problems bad enough for them to stop taking a medicine if they had been (assuming each event happens in a separate person).

"If all 1,000 took this treatment, 50 people will stop taking the treatment, five people will have a persistent liver disturbance, one person will have a potentially serious muscle problem and 944 people would have no problems bad enough for them to stop taking the treatment.

"In other words treatment probably causes an extra three harmful events (two liver disturbances and one muscle problem) in these 1,000 people over five years. You could be one of these three (harmed by treatment), or you could be one of the other three (harmed even without treatment) or one of the 994 (not harmed either way). Equally you could be one of the 50 that stops taking the medicine due to more minor side effects, or one of the 950 that does not."

Panel 3: A summary of the benefits to patients of lifestyle changes

- In a mixed Scandinavian population, even moderate consumption of wine was linked to relative risk reductions of around 20–25 per cent in all-cause mortality and 22–37 per cent for death from coronary heart disease, compared with not drinking at all.¹⁶
- In a non-hypertensive population, mean 47 years old, reduction of salt consumption by 3g a day probably reduces risk of death due to CHD by about 6 per cent.¹⁷
- In overweight and obese patients, a 10kg weight loss could result in a 20 per cent fall in total mortality and a 15 per cent fall in low-density lipoprotein cholesterol.¹⁸
- There is strong observational data that moderate levels of daily physical activity compared with a sedentary lifestyle lower the relative risk of CHD by about 30–50 per cent.¹² A study in a low risk group of healthy female nurses showed that those who walked for between one and three hours a week had a 30 per cent lower relative risk of major coronary events.¹⁹
- Observational studies show that in primary prevention patients increasing daily intake of fruit and vegetables by about 150g probably leads to a relative risk reduction of 20–40 per cent (but estimates do vary significantly).¹¹
- A study in Europeans free of coronary heart disease showed that an average intake of 17g of oily fish per day reduced the relative risk of CHD death by 34 per cent over 20 years compared with no consumption.²⁰

so did 5.1 per cent of the placebo group: no significant difference.

The harms we are most concerned about are liver enzyme disturbances and myopathy. In the Heart Protection Study the excess rate of alanine aminotransferase elevations greater than four times the upper limit of normal was 0.11 per cent; this reduced to 0.05 per cent for persistent elevations with 0.2 per cent more patients on simvastatin stopping treatment due to these problems. There were six extra cases of myopathy (with or without rhabdomyolysis) in simvastatin taking patients, an excess rate of 0.06 per cent.

These are the rates for the 40mg dose; with 10mg they would be expected to be lower, but we could use these as "worst case scenario" estimates even though in many cases the differences between simvastatin and placebo are not statistically significant.

How can this be explained?

So far we have managed to establish that simvastatin 10mg sold OTC will probably be of benefit to patients at 10–15 per cent risk over 10 years who take it regularly in the long-term. We have been able to arrive at quantifiable benefits and harms, although approximate and based on (reasonable) assumptions. Yet relative risk reductions and numbers needed to treat (NNTs) remain confusing to many health care professionals, never mind patients. It is absolutely essential that pharmacists understand the figures and are able to put this across in the consultation so that the patient can make an informed choice.

Clinical trials and our extrapolations from them provide us with evidence of mean effects across a population. With any intervention there will be a normal distribution of the magnitude of these effects: some patients will gain a lot more and others will gain much less

(and possibly even do worse), but most people will lie close to the mean. In the case of an individual we have no robust way to predict exactly what will happen to them; we can only explain the average.

It is also important to realise that, especially in low and moderate risk groups, many patients will not have a coronary heart disease event regardless of whether or not they take treatment. For example a 10 per cent risk over 10 years means that 10 per 100 patients will have an event or, in other words, 90 will not. Treatment will prevent some, but not all, events from happening.

Panel 1 shows a number of different ways of presenting the information estimated above that could be used to communicate the benefits to a patient (all are worked out on the average patient, ie, 12.5 per cent risk over 10 years). All of these are based on the same information and all are true representa-

tions of the estimates. Where possible we should probably use more than one explanation including pictorial methods. More information on risk and how to communicate it can be found in the medical literature although an excellent starting point is the themed issue of the *BMJ* published last year.¹⁵ Panel 2 repeats this process for the potential adverse effects.

What else needs to be covered?

In an editorial, *The Lancet* voiced concerns that patients may opt to swallow a pill rather than make appropriate improvements in their lifestyle,³ eg, stopping smoking, reducing intake of saturated fats and excessive calories or increasing their level of physical activity. This would be a serious worry if it occurred because these behaviours are not just beneficial in avoiding coronary heart disease events but also in reducing the risk, between them, of cancer, diabetes, chronic obstructive pulmonary disease, other vascular diseases (eg, stroke) and other serious health problems. It would be misguided to swap any of these changes for a daily pill. Pharmacists have a responsibility to advise patients on how to combine treatment with these interventions to their greatest benefit, just as doctors and nurses do with the groups they treat under the NHS.

To help provide context alongside the use of OTC simvastatin, Panel 3 provides a summary of the benefits of a number of lifestyle changes in patients similar to those who may be buying the medicine. These relative risk reductions should be compared with the estimated 24 per cent reduction in non-fatal myocardial infarction or death due to coronary heart disease with OTC simvastatin over five years, with no proven effect on all cause mortality.

The National Service Framework for Coronary Heart Disease²¹ puts this all in perspective: it is thought that about half of the decline in CHD death rates over the past 20 to 30 years is due to lifestyle changes and half due to better treatment and care. In other words the population, through their behaviour, hold as much influence over their risk of coronary heart disease as all of the NHS put together. Shared responsibility is crucial and this does not mean opting for a tablet rather than positive lifestyle action.

Conclusion

The reclassification of simvastatin 10mg as a pharmacy medicine is a hugely significant step for pharmacy. It is entirely appropriate that the basis for this decision is held up to scrutiny, but I hope this article has shown how logical analysis and extrapolation of the existing evidence base should give us confidence that the product will be effective. The choice now is whether individual patients feel strongly enough to spend their money and take the treatment regularly, long-term for an approximate 15 per 1,000 chance of benefit with a three per 1,000 excess risk of harm. Pharmacists have to ensure that their patients

are informed enough for this process to occur, but also that regardless of the patient's decision, they are encouraged and supported in lifestyle change.

DECLARATION OF INTEREST The author has received payment from the Royal Pharmaceutical Society to write practice guidance relating to the sale of over-the-counter simvastatin and has received funding from Merck Sharpe and Dohme in the past (support to attend a conference on osteoporosis and payment for participation in consultancy panels) but none related to OTC simvastatin.

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