Review of patients switched from atorvastatin to simvastatin after two years in a general medical practice

Abstract

Objectives: Achieve cost savings in statin prescribing in a general medical practice population, follow-up patients included, and evaluate clinical and biochemical outcomes.
Design: Switch a cohort of patients prescribed atorvastatin 10mg or 20mg to an equivalent dose of simvastatin. Monitor patients for two years in a prospective study to evaluate disease and patient-orientated outcomes.
Setting: The study took place in Primary Care in a practice of 4000 patients.
Participants: There were 134 potential patients on atorvastatin, 98 of whom were switched to simvastatin and evaluated over two years. Thirty-six patients were excluded because of factors such as intolerance to simvastatin or renal failure.
Main outcome measure: Thirteen of the 98 patients (13%) have reverted to atorvastatin; 79 are still taking simvastatin (81%) and six no longer take statins. There have been no adverse morbidity effects or any mortality. Cost savings amount to 5% of the annual practice budget.
Conclusion: The switch process was cost effective and more than 80% successful. This was achieved through judicious selection of appropriate patients, furnishing them with clear information and the option of a clinic consultation. This approach for the PCT has generated financial savings without compromising the health status of the population. Further, the pharmacist has played a part in the reinforcement of adherence to medication and lifestyle modifications, such that the patients' chronic disease is better controlled and s/he is less likely to have need of hospitalisation.

Aim

To achieve cost savings in statin prescribing without compromising health status in patients and maintaining beneficial clinical outcomes.

Objectives

1. Select appropriate patients at a practice, to switch from atorvastatin to simvastatin.
2. Monitor these patients' cholesterol readings three months after the switch, and thereafter at yearly intervals.
3. Assess the patients' clinical outcomes and surrogate markers after two years.
4. Calculate the actual cost savings as a result of the switch.

Introduction

The primary care practice, in common with all practices in the PCT, implemented a programme to switch suitable patients from medication with atorvastatin to simvastatin. GPs in the PCT favoured prescribing of atorvastatin as first-line statin, because of the belief that a patient's cholesterol would be reduced further and quicker with atorvastatin than by any other statin.

The planned switch was in response to the need for the PCT to achieve budgetary balance at the end of the financial year. The prescribing budget can be clearly targeted because it comprises consistent and predictable components. Our PCT required a saving of £2.8 million for the year. The annual spend on atorvastatin was £1.7 million. Thus there was considerable potential for savings in this drug class alone with simvastatin being up to 30 times cheaper than atorvastatin.

A study[1] has been conducted to show the initial impact of a switch from atorvastatin to simvastatin. This study now shows the longer term effect of such a switch to indicate the persistence of patients with the medication and the impact on long-term chronic disease management.

Background

Simvastatin and atorvastatin are the current main PCT statins. Simvastatin is now off patent whereas atorvastatin retains its patent until November 2011. Nationally, in 2004, statins accounted for 9.1% of NHS prescription costs (and in 2006–7 atorvastatin alone accounted for 8%) and these prescriptions are growing exponentially by 30% per year.[2] Simvastatin and atorvastatin are rated number 1 and 2 in terms of drug costs in England (£251million and £360million respectively). The simvastatin price fall will save more than £200million in England per year, but an equivalent or larger gain is available if patients taking atorvastatin 10mg or 20mg are swapped to an equivalent dose of simvastatin. The saving for the PCT would be approximately £900,000 (assuming patients taking atorvastatin 40mg or 80mg remain on these doses). Co-operation with the local district general hospitals will enhance this potential saving in the Trust.

NICE guidelines[3] propose statins for secondary prevention of cardiovascular disease (CVD) and primary prevention for people with a ≥20% 10-year cardiovascular risk. They also state that the statin with the lowest acquisition cost should be used. Initial estimates are the guidelines make 1 in 4 of the population aged 30 to 75 eligible and switching from atorvastatin 10mg or 20mg to simvastatin 40mg represents the largest single drug saving ever available to the NHS. This saving can be used to treat more patients, thereby reducing the overall cardiovascular disease burden.

Study rationale

1. Prescribing policy. In primary prevention, patients should take simvastatin first line unless they have very high initial cholesterol levels or are unable to tolerate simvastatin or have another contraindication.[3]

2. Equivalent doses. Where adequate lipid control is achieved on atorvastatin 10mg or 20mg, simvastatin 40mg will give about the same level of lipid control because they are approximately equivalent at these dosages.[4]

3. Lipid effects. Simvastatin 40mg has a larger HDL raising effect than any atorvastatin dose (10–80mg). Atorvastatin demonstrates a negative dose response curve for HDL; higher doses of atorvastatin being progressively worse.[5]

4. Diabetes. Current NICE guidelines recommend that as a minimum all patients who have TC >/= 5mmol/l or LDL-C >/= 3mmol/l and a history of CVD or a 10-year cardiovascular event risk of >20% should receive a statin[3] as well as patients with diabetes either aged over 40 years, or with other risk factors.[6]

5. Renal impairment. Neither atorvastatin nor simvastatin require dosage adjustment in renal impairment unless the patient is in severe renal failure (i.e. GFR < 10mls/min) when a small dose of simvastatin may suffice such as 10mg daily. In end stage renal failure, there are negative data with atorvastatin 20mg.[7]

6. Drug interactions. Simvastatin and atorvastatin are both metabolised by CYP3A4. Both therefore have the potential for the same, numerous drug-drug interactions. Most drug interactions elevate blood levels of simvastatin or atorvastatin. Although there are no hard data, if a patient is already taking atorvastatin 10/20mg, because of the similar metabolic pathways involved, swapping to simvastatin 40mg is unlikely to be an issue.

Study design

The practice computer records were searched to identify all patients being prescribed atorvastatin. The selection of simvastatin and dose used was based on a consideration of whether the patient was being treated for primary or secondary prevention.

All patients requiring secondary prevention of CHD or other atherosclerotic vascular disease would receive at least 40mg simvastatin daily. This is based on the evidence from the HPS.[8] Secondary prevention co-morbidities included: CHD, ischaemic stroke, TIA, diabetes and PVD. Secondary prevention patients taking atorvastatin 10 or 20mg only were considered for a switch to simvastatin. Patients taking atorvastatin 40mg or above had a history of acute coronary syndrome with a subsequent angioplasty plus stent, or had not reached their lipid targets on lower doses. For primary prevention patients taking atorvastatin 10mg it was agreed with the doctors at the practice that patients would be switched to simvastatin 20mg. These patients had historically been placed on a statin, not because of a CHD risk score of 15% or more over 10 years, but because of a diagnosis of primary hypercholesterolaemia or mixed hyperlipidaemia. Agreement was made that simvastatin doses could be titrated up to achieve the target lipid reduction required based on the baseline lipid profile of <5 mmol/l for total cholesterol or a 25% reduction, whichever is the greater. Patients included in the switch were sent letters informing them of the drug change (figure 1) and an information sheet explaining cholesterol, it's meaning and impact on a patient's cardiovascular health (figure 2).

Patients were invited to speak to the practice support pharmacist for clarification of any issues if they wished. The repeat prescriptions for these patients were changed such that unless the patient contacted us they would automatically receive the new drug at the next dispensing. The local community pharmacies were informed so that they could answer queries from patients such as the dose differential between atorvastatin and simvastatin. All patients were reviewed for baseline cholesterol measurements; those without a recent record were invited for a fasting lipid profile blood test. Liver function and cholesterol levels were measured between 6 and 8 weeks after the switch to simvastatin. Patients were subsequently monitored at one yearly intervals to assess changes in both disease and patient orientated outcomes. This study looks at the cardiovascular and lipid profile of patients switched from atorvastatin to simvastatin, at the two year mark

Exceptions

The following groups were not switched from existing statin treatment provided this was tolerated and cholesterol levels were controlled. These were patients:

- with evidence of previous intolerance to, or treatment failure with, simvastatin
- with familial hyperlipidaemia, or those with baseline fasting STC >8mmol/l
- who were under the care of a specialist lipid clinic
- taking atorvastatin 40mg or more per day; normally those who have had an Acute Coronary Syndrome (ACS), and/or an angioplasty with a stent
- taking a combination of a statin and another form of lipid-lowering therapy (such as fibrate or ezetimibe)
- taking warfarin, amiodarone, verapamil, azoles, protease inhibitors, ciclosporin, nefazodone, nicotinic acid (>1g daily) or long-term macrolide use

Dear Sir/Madam,
The Practice, in conjunction with other surgeries in Harrow and North West London Hospitals, are implementing a policy of prescribing Simvastatin as the cholesterol-lowering drug of choice for the majority of patients. The reasons for this change relate both to reducing costs for the NHS and providing the safest treatment option.
In this respect, we are proposing to change your current cholesterol-lowering medication to an equivalent dose of simvastatin on your next repeat prescription. You will need a blood test after 6 weeks to ensure that your cholesterol is at least as well controlled as on your previous medication (a form is enclosed for you to make an appointment at the appropriate time).
If you have any queries regarding this change, or any other aspect of your medication, you may speak to our Practice pharmacist, Geoffrey Watman, by booking an appointment at one of his medication review clinics. Alternatively, you may speak to one of the doctors or nurses.
A patient information leaflet is enclosed which explains all aspects of cholesterol control.

Yours sincerely

Doctors at XY Medical Practice

Figure 1. Letter sent to patients

Patient Information Leaflet: Simvastatin to lower your cholesterol and risk of heart disease

Choice of Simvastatin as your cholesterol-lowering drug (statin)
Treatment rationale

- Recent studies provide evidence that support the use of statins in a wide population at risk of heart and circulation problems including those with diabetes and in people of all ages
- The higher the baseline risk of heart disease the greater the absolute reduction in risk and the greater the likelihood of benefit from statin treatment
- A heart protection study demonstrated that simvastatin was effective in reducing the incidence of heart attacks and major circulation problems in a population of men and women of all ages.

What is Cholesterol?
Cholesterol is a fat present in your body and carried in the bloodstream. We absorb cholesterol from food. Some cholesterol is good and healthy, but too much cholesterol contributes to heart disease.

How does cholesterol cause heart problems?
High levels of cholesterol in the blood can, over many years, result in fatty deposits on the walls of blood vessels. As the vessels 'fur up', they get narrower. As the vessels narrow, less blood gets to the vital organs, including the heart. Angina, heart attacks and heart failure can occur when the vessels which supply blood to the heart are narrowed. Strokes can occur when blood vessels in the brain are narrowed and pain on walking (claudication) can occur when arteries in the legs are narrowed.

Who should have their cholesterol tested?

- People with cardiovascular disease, including heart disease, poor circulation and stroke patients
- People at risk from cardiovascular disease, which may be due to poor diet, lack of exercise, high blood pressure, smoking, obesity or diabetes
- People from families with a history of cardiovascular disease in a parent or sibling under 60 years
- People on cholesterol-lowering treatments.

Ways to reduce cholesterol
Reducing your level of cholesterol will prevent a further build-up of fat in the blood vessels and reduce the risk of heart disease. Cholesterol can be reduced in a number of ways:

- Diet. Avoid or reduce the consumption of fat (see separate sheet)
- Exercise. Take regular exercise, up to five times a week, for 30 minutes or more per session. Cycling, swimming, brisk walking or jogging are probably the best forms of exercise, but start gently and if you have other medical problems, e.g. arthritis, consult your doctor before beginning. Stop the exercise if it is painful or excessively uncomfortable. Some breathlessness on exercise is a good thing and demonstrates a good level of exertion
- Medicine. Even on a very low fat diet, many people will not attain the optimum target for cholesterol level, and your doctor will prescribe a medicine to suit you. Statin therapy is the usual approach, and simvastatin has been shown to significantly reduce the incidence of major heart problems.

Is it really worth taking the tablets?
Recent studies have conclusively shown that the lowering of cholesterol levels helps reduce the risk of heart attack and death amongst patients who have experienced certain heart problems.

What can I do to reduce my chances of heart disease?
There are a number of known causes of heart disease of which high cholesterol level is one of the most important. Other causes and ways of reducing the risk of heart disease:

- Diabetes. This often leads to heart disease. It is often associated with obesity, which, together with raised blood pressure and high cholesterol, may lead to cardiovascular disease. Diabetes can be controlled with a combination of weight loss, moderate exercise, diet and medicine
- Hypertension. High blood pressure is usually without symptoms, and it is advisable to routinely have a BP reading, with a nurse or pharmacist, in order to check for hypertension. High blood pressure is a major risk factor, and improves with lifestyle changes, salt restriction and anti-hypertensive drugs
- Smoking. This remains the single most common cause of heart disease and dramatically increases the risk of illness. Stopping smoking is the best thing you can do for your health. Ask your doctor or pharmacist for advice, and access the Harrow Smoking Cessation Service
- Excess alcohol. Although small amounts of alcohol may be beneficial to the heart, excessive consumption increases the risk of heart disease and many other diseases. Keep within no more than 2-3 units per day for women and 3-4 units per day for men. 1 unit is equal to a glass of wine, a half-pint of beer or one pub measure of spirits
- Obesity. Increased weight may lead to diabetes, which, in turn, may develop into cardiovascular disease. This is best controlled through weight loss, physical activity and a healthy diet
- Risk factors. It is important to consider and control all the risk factors, where possible, in each person to minimise the chances of developing heart disease or to prevent progress if already present.

Figure 2. Patient information leaflet

- with chronic renal failure, stage 1 or 2, in accordance with the preference of the hospital renal clinic
- in whom switching may compromise their compliance.

Results

There were 4009 patients in the practice at May 2006 and 134 were prescribed atorvastatin 10 or 20mg (PC1; Figure 3). Of these patients 44 had been put on atorvastatin for secondary prevention and 34 as a result of a diagnosis of diabetes mellitus or a cardiovascular risk score of 20% or more, over the next 10 years. Therefore, 78/134 patients could be considered as secondary prevention patients, i.e. 58% of the total cohort. The remaining 56 patients (42%) had either mixed hyperlipidaemia or essential hypertension as the only reasons for primary prevention. Ninety-eight patients were switched to simvastatin (PC2). Thirty-six patients remained on atorvastatin (PC3) and reasons for this are listed in Table 1. The status of patients switched to simvastatin was assessed in January 2009 (data are presented in Table 2). Reasons for reverting to atorvastatin are given in Table 3.

Fifty-five percent of patients persisting with simvastatin had IHD (21 patients) or diabetes (26) and they are all taking simvastatin 40mg daily. Forty-five percent were categorised as having hypertension (26 patients) or mixed hyperlipidaemia (12) and these are all taking simvastatin 20mg daily. There are now 47 patients

Table 1. Reasons for patients to remain on atorvastatin

Reason	Number of patients
Simvastatin intolerance or failure to reach STC target	8
Taking statin + fibric acid derivative	3
Renal failure	10
Patient taking warfarin	3
Directive after ACS +/- PTCA	9
Private Lipid Clinic	3
Total	36

taking simvastatin 40mg and 32 patients taking simvastatin 20mg, six of the original patients having stopped lipid therapy.

Clinical outcomes

Three of the IHD patients are now classified as having progressed to heart failure status, following ECHO and BNP measurements. Of the MHL patients two now have a diagnosis of aortic valve disease, but three have stopped statin therapy. Three of the diabetic patients reported atypical chest pain, which proved to be non-cardiac in origin. Four of the EH patients have some degree of left ventricular dysfunction, but three have now stopped statins. There was only one death in the simvastatin group, a lady in her nineties, with non-cardiac causes

Cholesterol readings taken before and after the switch were obtained for 79 out of the 85 patients who were switched.

Table 2. Status of patients switched to simvastatin*

Still taking simvastatin (PC4)	79
Not taking lipid-lowering treatment	6
Switched back to atorvastatin	13
Total	98

** January 2009*

The mean total cholesterol for all patients was 4.99mmol/l before the switch and 4.52mmol/l two years after the switch. There was an improvement in average HDL from 1.33mmol/l before the switch to 1.39mmol/l two years after the switch. The LDL readings reduced from a mean of 2.87 mmol/l before the switch to 2.42 mmol/l two years after the switch and triglyceride levels reduced from a mean of 1.80 mmol/l to 1.58 mmol/l.

Discussion

Morbidity and mortality

Encouragingly of the 85 patients who remained on simvastatin, there were no adverse cardiovascular clincal outcomes and six patients stopped statin therapy. Three of these had been diagnosed with EH and three with MHL as the only reason for the introduction of a statin and not for a justified CVD risk score in primary care. There was a tendency for GPs to prescribe a statin for a single cardiovascular risk factor when statins were first introduced in the 1990's.

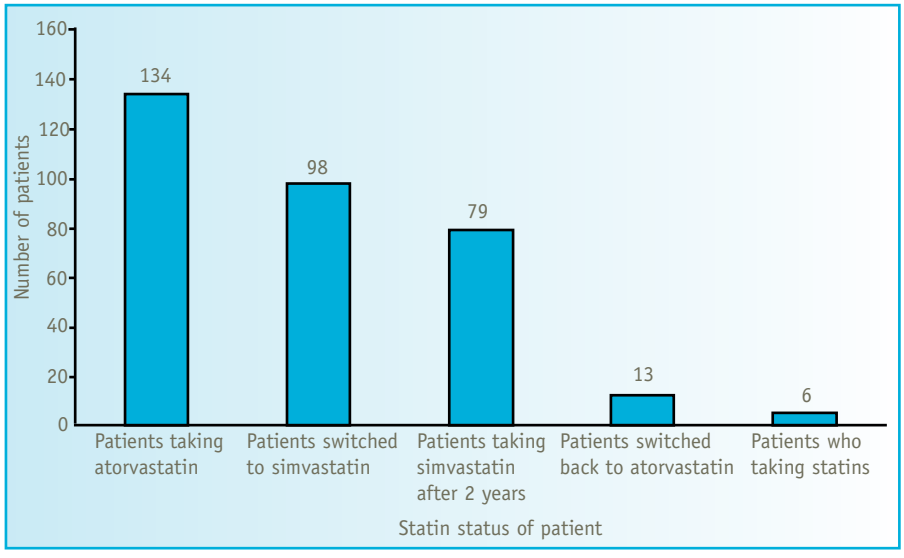

Figure 3. Consort diagram to show statin changes for original atorvastatin patient cohort (PC1)

Table 3. Reasons for patients reverting to atorvastatin

Not reaching cholesterol targets with simvastatin	5
Muscle aches and pains	3
Allergic reactions/ skin rash	4
Patient protest	1
Total	13

In the remaining atorvastatin cohort two patients died despite intensive therapy. These deaths are an indication that in practice the treated population is still at a relatively high risk of experiencing an adverse cardiac event or death. In a high risk population such as that assessed in the 4S study (patients with history of MI or angina and raised cholesterol despite diet) it was shown that 8% of patients died from a cardiovascular event during 5 years of follow up even though they were receiving active treatment.[9]

Cholesterol targets

The UK NSF for CHD, reiterated by the DOH, recommends that once the decision to lower cholesterol with a statin has been made serum total cholesterol (STC) should be lowered to <5mmol/l and LDL to <3mmol/l.[10] The JBS2 guidelines recommend lower optimum targets of STC 4mmol/l and LDL of <2mmol/l.[6] The study results confirm that despite treatment with a high intensity lipid-lowering agent in practice cholesterol levels rarely fall to JBS2 optimal levels, and that, for most people, simvastatin at 20mg or 40mg daily dose is sufficient, although clearly there is a limit depending on the actual target and baseline lipids.

For primary prevention NICE lipid modification guidance (CG67)[11] recommends that simvastatin 40mg, or a drug of similar efficacy and acquisition cost, should be offered as part of the management strategy for adults aged more than 40 years who have a 20% or greater 10-year risk of developing CVD. The majority of primary prevention patients at the practice were initiated with a statin on the basis of high cholesterol readings only and not a cardiovascular risk score. These patients are now treated with simvastatin 20mg daily,

and none, so far, have progressed to overt CVD.

In secondary prevention NICE recommends that a higher intensity statin is offered to people with ACS and to those who have had an angioplasty with a stent. If the total cholesterol does not fall below 4mmol/l or the LDL-C does not fall below 2mmol/l an increase of dose should be considered. However, as can be seen from the results, in practice the majority of patients do not achieve these targets. In the simvastatin cohort 20 out of 79 achieved an STC of <4mmol/l or an LDL-C of <2mmol/l. Of the patients taking atorvastatin, only 14 reached this target. The good cardiovascular status of these patients indicates that patient orientated outcomes are more important than disease ones.

Intensive lipid-lowering therapy

This study confirms that intensive therapy is not necessary for all patients, despite promising evidence for the following reasons:

1. In the TNT study,[12] the 'IDEAL' study,[13] and the Prove-It TIMI 22 trial[14] atorvastatin 80mg failed to reach the primary pre-specified endpoint with no mortality benefit. The recommended statin, simvastatin 40mg, is more potent than the low dose control arms employed in all three of these trials.
2. Intensive lipid lowering therapy results in higher discontinuation rates, adverse effects, more drug interactions and requires robust monitoring.
3. The incremental lipid lowering comes at significant additional cost.

Lipid effects

1. High density lipoprotein

The simvastatin patients showed an increase in HDL, which belies the belief that atorvastatin has the advantage of preferentially increasing HDL. In fact, simvastatin 40mg has a larger HDL raising effect than any atorvastatin dose (10–80mg). Atorvastatin demonstrates a negative dose response curve for HDL and higher doses of atorvastatin are progressively worse (STELLAR and CURVES studies).[4,5] This has been shown to be a good reason for convincing patients of the benefit of a switch.

2. Triglycerides

The study patients showed a mean reduction of 12% compared to previous therapy on atorvastatin. Thus, the notion of GPs in the PCT, that atorvastatin is more effective at lowering triglyceride levels is unfounded. This means that simvastatin can safely be substituted for atorvastatin without the risk of the adverse change in the quality of LDL and HDL molecules that a high triglyceride level may bring.

Diabetics

A sub-analysis of the 26 diabetic patients showed a change in average LDL-C from 2.12 to 1.94 mmol/l and a drop in average triglycerides from 1.71 to 1.58mmol/l respectively, on switching from atorvastatin to simvastatin. There is a belief among practitioners that atorvastatin is better for people with diabetes mellitus because elevated triglyceride levels are commonly seen in type 2 diabetes, but this is evidently not the case.

As a guiding principle in Type 2 diabetics NICE[3] recommend consideration of addition of a fibrate in patients with a history of CVD whose TG levels remain >/= 2.3 mmol/l after 6 months of (unspecified) statin therapy. It would now seem feasible that such patients could be considered for a switch to simvastatin without impairing lipid status.

Drug-drug interactions

Patients taking warfarin remained on atorvastatin, although, with close monitoring of INR, simvastatin could be safely introduced in future on an individual basis. Once stabilized, normal monitoring will suffice. Patients taking amiodarone or diltiazem were successfully switched without problem although only to simvastatin 20mg; none of the patients were taking verapamil.

Side-effects

Seven of the patients who reverted to atorvastatin did so because of undue side-effects. For a low/intermediate dose (atorvastatin 10/20mg, simvastatin 40mg) simvastatin and atorvastatin have minimal side-effects. Side-effects increase with dose, but it is not clear whether the side-effects increase with dose taken or lipid lowering effect. Patients tend to peruse drug information inserts when switched to an alternative drug; this may sensitise their intolerance to a new drug.

Primary care outcomes

1. QOF targets

The simvastatin group comprised 11 patients whose STC had fallen from >5mmol/l to <5mmol/l and only one who had moved in the other direction. The LDL of 15 patients was reduced from >3mmol/l to <3mmol/l whereas only two went back above target. This confirms the principle of a study by other investigators,[15] which indicates that QOF cholesterol targets, CHD,[8] stroke[8] and DM can be achieved in a practice at a lower cost with generic statins.

2. Patient adherence

Written, telephone and in some cases visual contact enabled patients to have a clear understanding of the progressive nature of atherosclerotic disease, their level of risk and the need to take prescribed drugs for the rest of their lives. Adherence to prescribed therapy is poor, compromising the therapeutic potential of long-term treatment with statins. Despite international guidelines recommending LDL-C goals and the availability of effective statin therapy, optimal prescribing and response does not always take place.[16] Improvement of adherence to achieve clinical aims is therefore a goal for health care professionals.

Cost savings

Seventy-nine patients have remained on simvastatin 20 or 40mg after a switch from atorvastatin 10 or 20mg. This represents an annual, ongoing saving of £22,000 per annum, for a practice whose budget is £440,000, representing a saving of 5%.

The price of simvastatin has fallen spectacularly, beyond that usually associated with a drug coming off patent. Atorvastatin is the number one drug cost in England,

and 85% of tablets are at 10mg or 20mg. Nationally, replacing atorvastatin 10/20mg with simvastatin 40mg would, based on the 2007 spend on atorvastatin 10mg and 20mg, reduce costs from £360million to £47million per year.

Summary

The principle of the switch process in this study has been replicated throughout the UK PCTs freeing essential money for other health care provider resources. The ultimate aim is improved and consistent patient care, by provision of information and support to patients, such that optimisation of their prescribing does not impair adherence to their medication spectrum.

Practice support pharmacists are well placed to assess the practicality of any proposed switch of drugs, taking into account the patent expiry date of the higher cost drug and the potential cost savings. Pharmacists are able to conduct patient searches, make initial selection of patient cohorts for ratification by their GPs and implement the switch process. Further, as this study shows, they provide a time- and cost-efficient monitoring process.

Declarations of interest

The author has no interests to declare.

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