# Simvastatin: building on success

*Allan Gaw*

***Over a decade after launch, simvastatin remains the most widely-prescribed statin in the UK. This has resulted from a growing body of long-term outcome data, a steadily expanded range of indications, an extended dose range and proven cost-efficacy.***

Simvastatin (Zocor®, Merck Sharp & Dohme, Hoddesdon) was the first statin to be launched in the UK in 1989, and today remains the most widely prescribed drug of its class, with over half a million patients benefiting from treatment. This reflects the established clinical tolerability and cost-efficacy of the drug which, with the publication of the landmark Scandinavian Simvastatin Survival Study (4S) in 1994, became the first lipid-lowering agent proven to reduce morbidity and mortality in patients with coronary heart disease (CHD), as well as being safe in long-term use. In that study, simvastatin was shown to reduce risk of overall mortality by 30% compared with placebo, risk of coronary mortality by 42% and major coronary events by 42%.

These long-term outcome data have led two influential bodies, the Standing Medical Advisory Committee (1997) and the Scottish Intercollegiate Guidelines Network (2000), to comment specifically on the use of simvastatin for secondary prevention of CHD.

## A GROWING BODY OF CLINICAL DATA

Since their initial publication, the original 4S data have been re-analysed to demonstrate additional attributes of simvastatin in the secondary prevention of CHD:

- A reduction in the development of new or worsened angina pectoris by 26%, and a reduction in the development of new or worsened signs and symptoms of intermittent claudication by 38% (Pedersen et al, 1998).
- In patients with clinical diabetes, a significant decrease (42%) in the risk of major coronary events. In patients with impaired fasting glucose, a significant decrease (55%) in the risk of coronary mortality, total mortality (43%) and of major coronary events (38%) (Haffner et al, 1999).
- A reduction in the risk of major coronary events in both women and the elderly. In patients over the age of 65 years, simvastatin has been shown to halve the absolute risk of mortality compared with younger patients (Miettinen et al, 1997).

An extension study of 4S, recently published in the *American Journal of Cardiology* (Pedersen et al, 2000), involved 2 672 patients from the original trial treated for a further 2 years. This confirmed that the 30% reduction in mortality observed was safely maintained for up to 8 years. Over the 2-year period, 4.9% of patients from the original placebo group and 3.6% from the original simvastatin group died. Combined with the original 4S results, over a total of 8 years 15.9% of patients originally assigned to the placebo group died, compared with 11.5% of patients originally assigned to the simvastatin-treated group. The increased survival was also evident among those patients aged 65 years or over, in whom risk of death was reduced by 28% (*Figure 1*). This is the longest period in which the benefit of reduced mortality has been demonstrated with a statin.

## EXPANDED INDICATIONS

In October 1998, simvastatin was licensed for raising high density lipoprotein cholesterol (HDL-C). This was based on the findings of 4S, which showed an 8% rise in HDL-C, observed at week 6 and maintained over the full 5.4 years of the study. This was shown to be significantly correlated ($P$=0.039) with the reduction in risk of major coronary events observed.

Evidence for the effect of simvastatin on HDL-C levels was further reinforced with the

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results of a study presented at the International Symposium on Atherosclerosis meeting in June 2000. In 826 patients with low density lipoprotein cholesterol (LDL-C) above 4.1 mmol/litre and triglycerides less than 3.9 mmol/litre, simvastatin 80 mg was shown to be significantly superior to atorvastatin 80 mg in raising levels of HDL-C over a 36-week period (7.6% *vs* 3.1%, $P<0.001$). Simvastatin 80 mg was also shown to raise levels of apolipoprotein A-1 (apo A-1) by 2.5%, compared to a decrease of 3.5% seen with atorvastatin 80 mg over the same period ($P<0.001$) (Merck Sharp and Dohme, unpublished observations, 2000). apo A-1 levels are inversely related to the risk of CHD.

At the same doses, 10.4% (41 of 394) of patients taking atorvastatin experienced gastrointestinal side-effects compared to 3.4% (13 of 385) of patients taking simvastatin ($P<0.001$), and 3.8% (15 of 392) of patients taking atorvastatin experienced liver-related side effects, compared to 0.5% (2 of 384) of patients taking simvastatin ($P=0.002$) (Merck Sharp and Dohme, unpublished observations, 2000) (*Figure 2*).

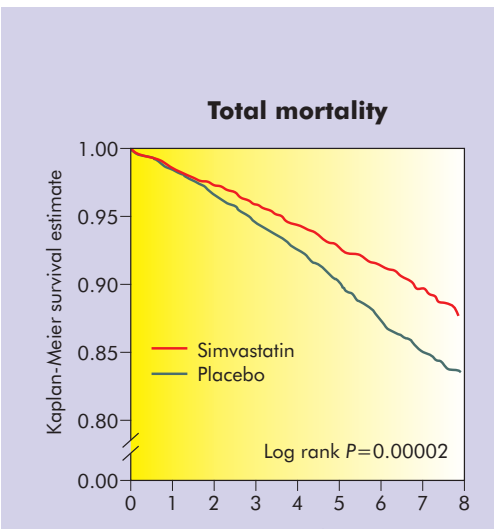


*Figure 1. Kaplan–Meier curves for all cause mortality. From Pedersen et al (2000).*

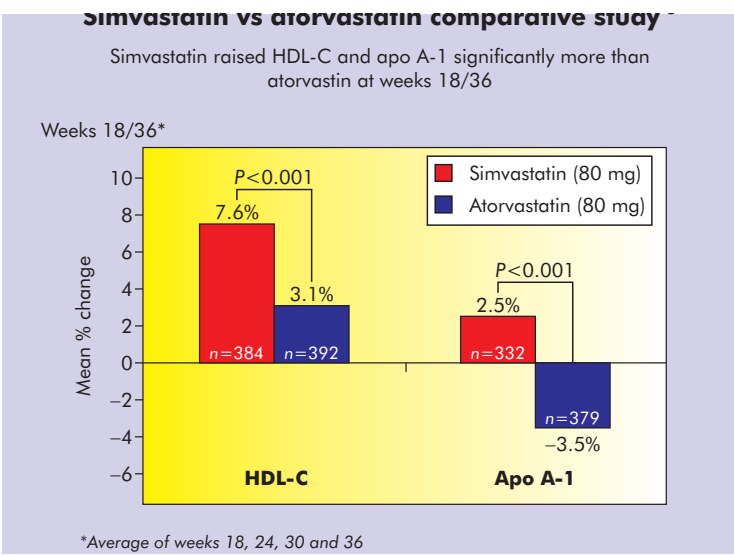


*Figure 2. Simvastatin vs atorvastatin comparative study*. From Ose et al (1998). apo A-1 = apolipoprotein A-1; HDL-C = high density lipoprotein cholesterol.*

## EXTENDED DOSE RANGE

In March 2000 an 80 mg tablet formulation of simvastatin was launched, offering additional lipid-lowering efficacy for those patients not sufficiently controlled by the commonly-prescribed doses of simvastatin and other statins. Importantly, this higher dose has been priced the same as the 20 mg and 40 mg doses.

Simvastatin 80 mg has been studied in trials involving 1105 patients over 6 months. It has been shown to lower LDL-C by 48%, total cholesterol by 37% and triglycerides by 38% in patients with elevated triglycerides. HDL-C was also raised by 10%. A combined total of one quarter of all patients taking simvastatin 80 mg experienced reductions of 55% or greater in LDL-C, making this new dose particularly useful for patients not controlled on lower doses of other statins (Ose et al, 1998).

## PROVEN COST-EFFICACY

Increased statin use advocated by the National Service Framework (NSF) for Coronary Heart Disease has highlighted the need for cost effectiveness. The NSF recommends that patients with established CHD should receive a statin to lower their cholesterol to less than 5 mmol/litre or by 30%, whichever is the greater (Department of Health, 2000).

A realistic method of calculating cost-efficacy is to compare the cost of statin doses required to maintain cholesterol at NSF-recommended levels, as the key cost pressure on primary care groups must surely come from maintenance prescribing.

This was done in a recent study, which took existing data from a European controlled clinical trial. The European trial had assessed the doses of various statins required to maintain LDL-C levels below the NSF recommended levels in cardiovascular hyperlipidaemic patients for a year. The mean annual cost of each treatment strategy was then calculated by applying UK basic NHS drug prices (March 2000) to the pro-

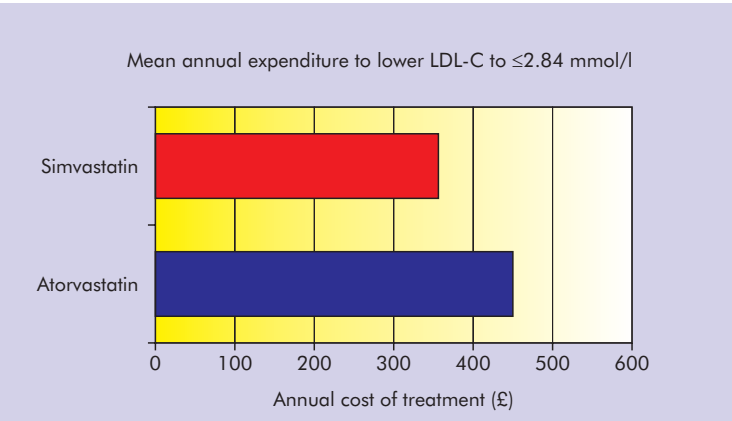


***Figure 3. Comparative UK cost efficacy of simvastatin and atorvastatin. From Phillips et al (2000). LDL-C = low density lipoprotein cholesterol.***

portions of patients maintained at each dosage step at the end of the study.

Results showed that significantly more patients achieved target cholesterol levels on simvastatin and atorvastatin than they did on either fluvastatin or pravastatin. Both the former were equally effective in maintaining patients to target cholesterol levels; however, the mean annual maintenance was significantly less for simvastatin *vs* atorvastatin: £358 *vs* £448 ($P<0.02$) (Phillips et al, 2000) (*Figure 3*).

## MORE TRIALS IN PROGRESS

Important new clinical data on simvastatin will continue to emerge in future years, as a result of two very large ongoing clinical trials: the Heart Protection Study (HPS) and the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH).

HPS, one of the largest controlled clinical trials ever conducted, is looking at more than 20 000 participants over a 5-year period. It will determine the long-term effects of simvastatin on both morbidity and mortality in larger numbers and a broader range of 'at risk' patients than any other statin trial to date: CHD patients with relatively normal cholesterol levels, women, the elderly and diabetics. The study is expected to conclude by 2001.

SEARCH will assess if there are any additional cardioprotective effects of simvastatin 80 mg *vs* the 20 mg dose used in 4S in 12 000 post-myocardial infarction patients. The rationale for this study is that a further additional reduction in blood cholesterol of about 0.5 mmol/litre achieved with simvastatin 80 mg may produce a 15–20% further reduction in CHD.

## BUILDING ON SUCCESS

With this growing body of clinical evidence for a positive effect on long-term outcomes, enhanced lipid lowering of the 80 mg tablet and proven cost-efficacy, simvastatin at doses of up to 80 mg once daily should be regarded as a first-line lipid-lowering drug for the effective reduction of cardiovascular disease. **HM**

*Conflict of interest: Merck Sharp & Dohme has funded Dr Gaw's attendance at scientific meetings and provided independent research grants to his department.*

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## KEY POINTS

- Over a decade after launch, simvastatin remains the most widely prescribed statin in the UK.
- Simvastatin has been shown to consistently reduce mortality for up to 8 years — the longest period this has been demonstrated by any statin.
- Simvastatin achieves significantly greater elevation of high-density lipoprotein cholesterol than an equivalent dose of atorvastatin.
- The mean annual maintenance cost associated with reducing cholesterol levels to a target similar to the UK National Service Framework target is significantly lower with simvastatin than atorvastatin.