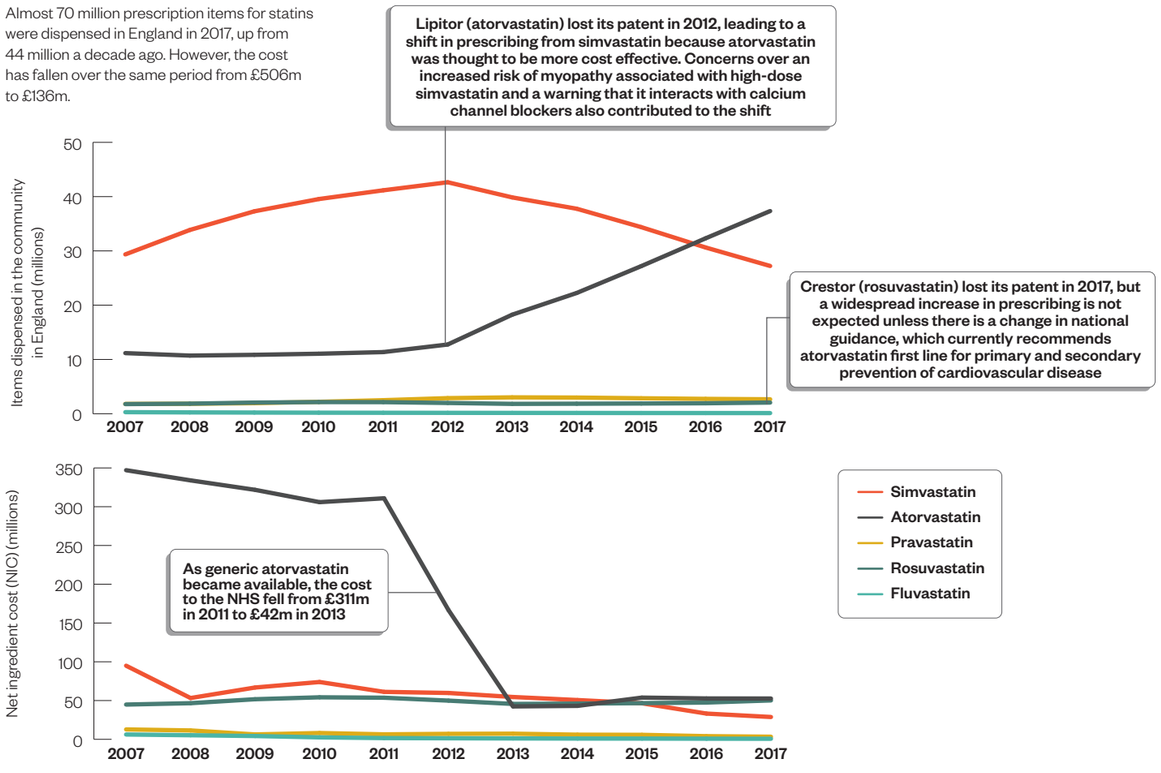
STATINS: THE HIGHS AND THE LOWS

Negative press seems to follow statins, the most prescribed drugs in England, despite them revolutionising cardiovascular disease prevention.

DAWN CONNELLY

A DECADE OF DISPENSING

Almost 70 million prescription items for statins were dispensed in England in 2017, up from 44 million a decade ago. However, the cost has fallen over the same period from £506m to £136m.



Source: NHS Digital

BENEFITS VERSUS RISKS

Data from two decades of studies show that the benefits of statins outweigh their risks, particularly for those at high risk of cardiovascular disease (*Lancet* 2016;388:2532).

If **10,000** patients are treated for **5 YEARS** with an effective statin regimen:

1,000 heart attacks and strokes would be prevented in those at high risk (i.e. secondary prevention)

500 heart attacks or strokes would be prevented in those at low risk (i.e. primary prevention)

50–100 cases of symptomatic adverse events (e.g. muscle pain or weakness) would be caused

50–100 new cases of diabetes would be caused

5–10 haemorrhagic strokes would be caused

5 cases of myopathy would be caused, one of which might progress to rhabdomyolysis

TRIALS AND TRIBULATIONS

1976 The first statin — **compactin** — is isolated from *Penicillium* mould by a research group working at Sankyo Pharmaceuticals in Tokyo, headed by Akira Endo.

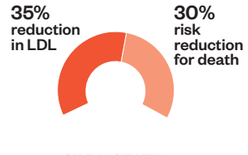
1979 After obtaining samples of compactin from Sankyo, pharmaceutical company Merck independently isolates a new 3-hydroxy-3-methyl-glutaryl-CoA (HMG CoA) reductase inhibitor, **lovastatin**, from *Aspergillus* mould.

1988 Merck develops a more potent semi-synthetic derivative of lovastatin, named **simvastatin**, which is launched in the UK the following year.

1990 **Pravastatin**, derived by a biotransformation of compactin, is developed by Sankyo and approved in the UK.

1994 The landmark **Scandinavian Simvastatin Survival Study (4S)** is published, which suggests simvastatin is associated with a 35% reduction in low density lipoprotein (LDL) cholesterol and a 30% relative risk reduction for death in people with established coronary heart disease and high cholesterol (*Lancet* 1994;344:1383).

Fluvastatin is licensed in the UK.



1995 The first primary prevention trial — the **West of Scotland Coronary Prevention Study (WOSCOPS)** — is published, showing that treatment with 40mg of pravastatin for five years in 1,000 middle-aged men with hypercholesterolaemia will save seven deaths from cardiovascular disease (CVD), two deaths from other causes, 20 non-fatal myocardial infarctions (MIs), eight revascularisations and 14 angiograms (*NEJM* 1995;333:1301).

1996 **Atorvastatin** is licensed in the UK.

2002 **The Heart Protection Study (HPS)** confirms the efficacy and safety of statins in a five-year trial of over 20,000 high-risk adults aged 40–80 years. It shows that statins benefit a wider range of people than originally thought, including those with diabetes, those who have had a stroke and those with normal cholesterol levels, without an increase in cancer or hospitalisations for non-vascular causes (*Lancet* 2002;360:7).

2003 The **Anglo-Scandinavian Cardiac Outcomes Trial — Lipid-Lowering Arm (ASCOT-LLA)**, a primary prevention study in a hypertensive population comparing atorvastatin 10mg with placebo, is terminated early because of a large treatment effect — a 36% reduction in the primary endpoint of non-fatal MI and death from coronary heart disease (*Lancet* 2003;361:1149).

Rosuvastatin is licensed in the UK.

2004 Johnson & Johnson MSD introduces an over-the-counter 10mg dose of simvastatin (**Zocor-HeartPro**), targeting those with a 10–15% risk of a cardiovascular event over ten years. However, the product is discontinued in 2010 owing to lack of consumer demand.

2005 The **Treating to New Targets (TNT)** trial shows that in patients with stable coronary heart disease, atorvastatin 80mg significantly reduces the risk of major cardiovascular events compared with low-dose atorvastatin (*NEJM* 2005;352:1425).

2006 The **National Institute for Health and Care Excellence (NICE)** issues its first guidance on statin use for the prevention of cardiovascular events, recommending it for people who already have CVD, whose ten-year risk of developing CVD is 20% or greater, or whose risk is increased because of diabetes or by being in high-risk ethnic groups.

2008 The **JUPITER** trial shows that rosuvastatin 20mg significantly reduces incidence of major cardiovascular events in healthy adults without high cholesterol but with elevated C-reactive protein, an inflammatory biomarker (*NEJM* 2008;359:2195).

2010 The **Cholesterol Trialists' Collaboration (CTT)** publishes a meta-analysis of data from over 170,000 participants from 26 randomised controlled trials demonstrating that more intensive statin therapy is associated with a significant further reduction in CVD events of 15%, with no increase in non-cardiac deaths or incident cancer (*Lancet* 2010;376:1670).

2013 Two articles are published that suggest the side effects of statins may outweigh the benefits for those at low risk, which kicks off a **media storm** in the UK. The following year, the authors of one of the papers withdraw a statement about the number of patients who suffer from statin-related side effects (*BMJ* 2013;347:f6123 and f6340).

2014 A change in the **NICE guidelines** for the primary prevention of cardiovascular events lowers the threshold for prescribing statins from a 10-year risk of cardiovascular events of 20% to 10%, fuelling the controversy over statins since this would include almost all men aged over 60 years and all women aged over 75 years.

2016 A **review** examining 30 years' of research into statins concludes the benefits of the drugs have been repeatedly underestimated and the side effects exaggerated (*Lancet* 2016;388:2532).

An **analysis** estimates that 200,000 patients stopped taking statins within six months of the media coverage of side effects and that this will result in between about 2,000 and 6,000 cardiovascular events occurring during the subsequent decade that would otherwise have been avoided (*BMJ* 2016;353:i3283).

2017 The suspicion that statin side effects originate from nocebo responses is given a boost with publication of the **ASCOT-LLA**, which shows no difference in adverse event reports between statin and placebo groups during the blinded phase but a 41% increase in muscle-related pains during the open label phase (*Lancet* 2017;389:2473).

2018 An **observational study** suggests that statins are not beneficial for healthy people aged over 75 years without type 2 diabetes mellitus (*BMJ* 2018;362:k3830).

Editorial advisers: Alison Warren, consultant pharmacist in cardiology, Brighton and Sussex University Hospitals NHS Trust and Brighton and Hove CCG; Paul Wright, lead cardiac pharmacist, St Bartholomew's Hospital, London
Infographic: nicolahawesdesign.com