Rosuvastatin: winner in the statin wars, patients' health notwithstanding

Rosuvastatin is one of the world's biggest selling branded drugs. Yet the evidence of its health benefits has always been weak and there is growing evidence of harmful side effects. **Sidney Wolfe** explains why he thinks the drug should have been withdrawn and why it should not be used

Last year, rosuvastatin (Crestor) was the most prescribed brand name drug in the US, with 22.3 million prescriptions filled and $5.8bn (£3.9bn; €5.5bn) in sales.[1] Worldwide 2013 sales were $8.2bn, the third highest for any branded drug.[2] Given the longstanding, continuing evidence of rosuvastatin's comparative lack of clinical benefits and increasing evidence of risks, how did this happen? The short answer is that of statins still on the market, the milligram for milligram cholesterol lowering potency of rosuvastatin exceeds all others, a fact exploited in advertising campaigns. But what about actually improving health, preventing heart attacks and strokes?

Less evidence of clinical benefit since approval

When rosuvastatin was approved in the US in 2003 for lowering cholesterol, three other statins—simvastatin, pravastatin, and lovastatin—had already obtained additional Food and Drug Administration approval for use to reduce cardiovascular risk, and a fourth, atorvastatin, was found to have such clinical benefit in 2004.[3]

But rosuvastatin did not gain approval for cardiovascular risk until 2010, and then only for primary prevention of heart attacks and strokes. Approval was based on the results of the JUPITER study, which included only patients with both low density lipoprotein (LDL) cholesterol <130 mg/dL (3.4 mmol/L) and C reactive protein ≥ 2 mg/L (19 nmol/L)[4] and thus has limited generalisability.

Other criticisms of the study include concern that the size of the treatment benefit could have been exaggerated because the study was stopped early.[5] Simulations show that trials stopped early will consistently overestimate treatment effects. This is supported by a study comparing the size of the benefits in 91 randomised controlled trials that were stopped early or truncated with those in 424 non-truncated trials, matched for the same disease research questions. The pooled results showed that trials stopped early for benefit "systematically overestimate treatment effects for the outcome that precipitated early stopping," especially with studies stopped with fewer than 500 clinical events.[6] When JUPITER was stopped early because of benefit, the accrued number of clinical events was 393.[2] The relatively larger effect seen in JUPITER than other statin trials is almost certainly at least partly because it was stopped early. A reduced benefit might be outweighed by the risks of rosuvastatin.

SPL

Rosuvastatin is the only statin in which rhabdomyolysis was detected in RCTs before the drug was approved

By the time rosuvastatin was approved for primary prevention in 2010, the three most prescribed statins had been approved for both primary and secondary prevention after multiple trials, including in patients with raised LDL cholesterol, had shown benefit (atorvastatin, four trials; pravastatin, three trials; and simvastatin, two trials).[3]

More evidence of risks

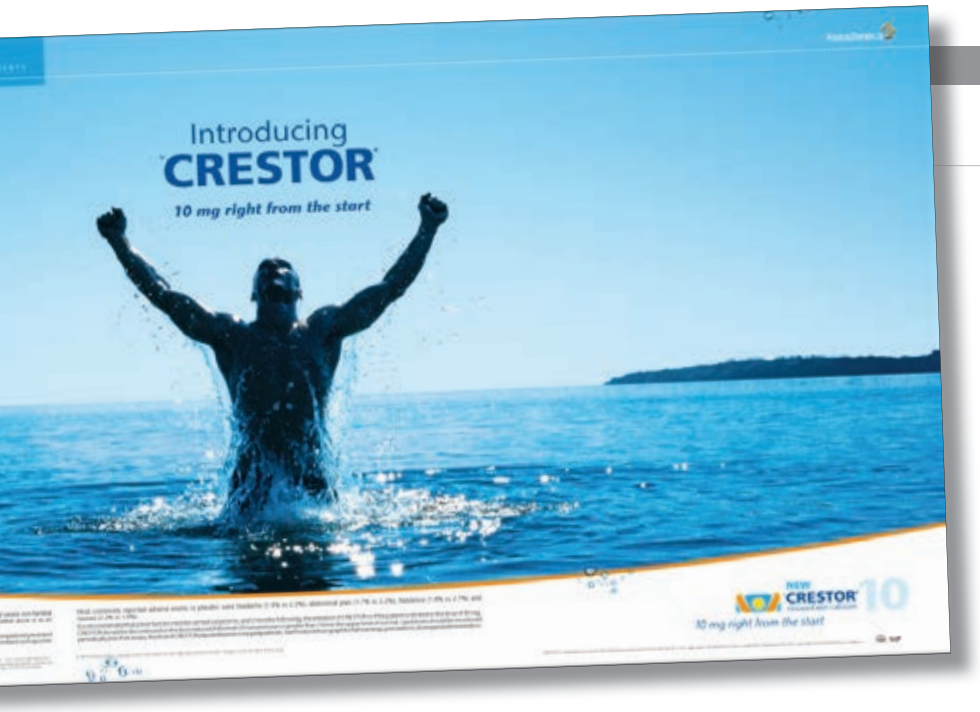
In addition to the evidence of clinical benefits for rosuvastatin being substantially less robust than for these three statins, there is increasing evidence that the drug also carries a higher risk of serious adverse effects. Prespecified outcomes in the JUPITER study[2] included not only cardiovascular endpoints but also new onset diabetes. Ironically, the reason for including this "hopeful" endpoint was that an earlier study had found that pravastatin decreased new onset diabetes.[7 8] In JUPITER, however, there was a significantly higher incidence (26%) of new onset diabetes in the rosuvastatin group compared with the placebo group.

A recent review of 17 randomised trials involving 113 394 patients comparing the risk of new onset diabetes for various statins corroborated this finding.[9] Treatment with rosuvastatin, compared with placebo, was associated with a 25% relative increase in the risk of developing diabetes; pravastatin was associated with the lowest risk, a 7% increase. An earlier, observational study of 240 000 patients beginning statin treatment also found that rosuvastatin was associated with the highest increased risk of diabetes and pravastatin the lowest.[10]

The differences in new onset diabetes are probably caused by the differing metabolic effects of rosuvastatin and pravastatin. In another randomised study of patients with raised cholesterol, rosuvastatin significantly increased glycated haemoglobin (HbA_{1C}) and fasting insulin levels, and decreased insulin sensitivity, whereas pravastatin significantly lowered HbA_{1C} and fasting insulin levels, and increased insulin sensitivity.[11] Further evidence of differing metabolic effects among statins has been recently reviewed.[12]

Rosuvastatin's FDA approved labelling now says: "In JUPITER, there was a significantly higher frequency of diabetes mellitus reported in patients taking rosuvastatin (2.8%) versus patients taking placebo (2.3%)."[13] The labelling for other statins merely states that "Increases in HbA1c and fasting serum glucose levels have been reported with HMG-CoA reductase inhibitors."

Other serious problems were identified before rosuvastatin's approval. Public Citizen opposed approval of rosuvastatin in 2003,[14] and in 2004 it asked the FDA to ban the drug because of two serious adverse reactions.[15] The first was



AstraZeneca spent an estimated $1 billion on the first year promotional campaign for rosuvastatin

rhabdomyolysis. Rosuvastatin is the only statin in which rhabdomyolysis was detected in randomised controlled clinical trials before the drug was approved. Even with cerivastatin, eventually banned because of rhabdomyolysis, no cases had occurred in the clinical trials before its approval. In a recent study of 641 703 patients in the UK prescribed different statins, those taking rosuvastatin had a significantly higher risk of an abnormally raised creatine phosphokinase activity than patients on large daily doses of other statins (simvastatin, pravastatin, or atorvastatin).[16]

The second serious concern seen during pre-approval trials was renal problems. At the time, rosuvastatin was the only statin to have been associated with proteinuria and haematuria. According to FDA documents "in the subgroup of patients with dipstick [protein and blood] positive urine, the percentage of patients with an increase of serum creatinine of 30% over baseline was 14%, 16%, 24%, 33%, and 41% for 5 mg, 10 mg, 20 mg, 40 mg and 80 mg of rosuvastatin, respectively. . . These data suggest that some patients with greater levels of proteinuria and hematuria may progress to clinically relevant renal disease."[17]

Although the FDA rejected our petition to ban rosuvastatin in 2005, the agency agreed that: "In addition, urine abnormalities, specifically proteinuria and hematuria, not previously noted in the review of other statin drug applications and not known to occur with this class, were observed sporadically in a small percentage of rosuvastatin-treated patients, with the highest incidence occurring at the 80-mg dose."[18]

Further concerns about rosuvastatin's renal effects were seen in an AstraZeneca funded randomised study comparing high dose rosuvastatin with atorvastatin in diabetic patients with progressive kidney disease.[19] Although rosuvastatin lowered plasma lipid concentrations to a greater extent than atorvastatin, the study reported that "atorvastatin seems to have more renoprotective effects." Urinary protein excretion was reduced during one year of treatment with atorvastatin 80 mg, with no significant changes in estimated glomerular filtration rate (eGFR). In patients given rosuvastatin 40 mg, however, "urinary protein excretion was not significantly different from baseline, but the patients did have a significant decrease from baseline in eGFR, and doubling of serum creatinine and acute renal failure were more common in this group."[19]

Why the drug remains popular

Given the evidence of more serious risks and less clinical benefit than other statins how has the drug fared so well for so long?

A prescient answer can be found in an October 2003 *Lancet* editorial, "The statin wars: why AstraZeneca must retreat."[20] It stated that AstraZeneca's chief executive, Tom McKillop, "has pledged to do whatever it takes to persuade doctors to prescribe rosuvastatin, including launching an estimated $1 billion first-year promotional campaign. 'We've got to drive the momentum,' he [McKillop] said at a recent investors meeting. 'You get one shot at launching a major new product. This is our shot.'" The editorial concluded, "Physicians must tell their patients the truth about rosuvastatin—that compared with its competitors, rosuvastatin has an inferior [clinical] evidence base supporting its safe use. AstraZeneca has pushed its marketing machine too hard and too fast. It is time for McKillop to desist from this unprincipled campaign."

McKillop promptly responded, accusing the journal of not telling the truth, then stating "Crestor is an extensively studied and well tolerated drug with a safety profile comparable to other marketed statins combined with a greater ability to get patients to their cholesterol goals than any other single product." Referring to the unmet need for adequate treatment with lipid lowering treatment, McKillop stated that "With this compelling medical need, it is unthinkable that we should desist from our efforts to make this medicine more widely available to physicians and patients."[21]

For the sake of the public's health, we must hope that the drug's disadvantages will lead to a sharp decline in its use

Barely more than a year later, in December 2004 the US FDA had to send a letter to AstraZeneca demanding that it immediately stop an advertisement in the *Washington Post* containing false and misleading information about Crestor's risks. The advert stated that "The scientists at the FDA who are responsible for the approval and ongoing review of CRESTOR have, as recently as last Friday, publicly confirmed that CRESTOR is safe and effective; and that the concerns that have been raised have no medical or scientific basis," citing the FDA website, which actually contained no such information.[22]

The advert was in response to a *Washington Post* article about Public Citizen's campaign against the drug, discussing the safety concerns shared by us and the FDA.[23] In the article Steven Galson, acting director of the FDA's Center for Drug Evaluation and Research, stated that the FDA "has been very concerned about Crestor since the day it was approved, and we've been watching it very carefully." He further stated the agency is "concerned about the same issues with Crestor as Public Citizen."

The FDA's letter to AstraZeneca said, "The 'patient safety' print ad makes false or misleading safety claims that minimize the risks associated with Crestor, thereby suggesting that Crestor is safer than has been demonstrated by substantial evidence or substantial clinical experience." The agency wrote to the company again the following year about "misleading superiority claims" for Crestor in other promotional materials.[24]

When patents expired for simvastatin, pravastatin, and atorvastatin, the rise in generic prescriptions quickly equalled or exceeded the sharp decreases in brand name prescriptions (IMS Health data). The patent for rosuvastatin expires in 2016, and with it AstraZeneca's need to promote it. But for the sake of the public's health, we must hope that the drug's disadvantages will lead to a sharp decline in its use before next year.

Sidney Wolfe senior adviser, health research group at Public Citizen, Washington, DC, USA
swolfe@citizen.org

Cite this as: *BMJ* 2015;350:h1388

"No one said to me this is a world you cannot enter"

Clare Marx, first female president of the Royal College of Surgeons of England, talks to **Luisa Dillner** about why she got the job and what she hopes to achieve

If Clare Marx is tired of being asked what it is like to be the first woman president of the Royal College of Surgeons of England, she is too gracious to show it. Her response is to show me how, since she took on the role in July last year, she has replaced the pictures of dead men that framed her presidential office with those of women surgeons who are very much alive. She works mostly in the small, modern room next door.

Marx's election in April 2014 was the first in the college's 214 year history in which members of the college council took part in a regular voting process. "Before then it was like voting for the pope," she explains. "You went into this room, and names emerged from the voting papers until someone was selected." Ten people stood, and Marx won. Was she surprised?

Apparently not. "The college was changing," she says, "It would be nice to think I was the best person for the job, but I suspect there was something about 'what does it say about us if we are ready to take a risk to make a change?'" Her voice goes quieter. "Or maybe it was because they thought I was the best person for the job."

Getting more women into surgery

Marx says that she has never thought of herself as a female surgeon. She was simply a surgeon. "No one said to me this is not a world you can enter. I had no negative feedback, just what I regarded as teasing, or maybe I am just blind."

She repeatedly says she has been lucky: in her career, in being president of the college, in finding good role models, and in having the support of her parents and husband. "It has taken me a really long time to realise that other people may need help," she admits, "and I don't mean that to sound patronising."

She decided to stand for president of the college "out of a desire to make a difference to delivering healthcare and to what surgery looked like as a career for women," she says.

"If we do nothing now it will take another 50 years to get the numbers of women up in surgery. We really need to work out how we support people to fulfil their full potential, and most people won't do it on their own."

Marx had a natural inclination for medicine from an early age. "My mother always says I was insatiably curious about people's health as a child," she recalls. "I partly chopped the end of my finger and was taken to accident and emergency; instead of sitting there like a wimpish child I went round the waiting room asking everyone what was wrong with them."

Her mother arranged some work experience for her with a surgeon in Coventry and she was smitten. Marx became interested in orthopaedics at the Middlesex Hospital and went on to be a consultant orthopaedic surgeon at St Mary's Hospital in London and then associate medical director at Ipswich Hospital.

> If we do nothing now it will take another 50 years to get the numbers of women up in surgery. We really need to work out how we support people to fulfil their full potential

Training and the 48 hour week

Marx is aware that training in surgery is in need of reform. But she supports the recommendations of the college (published last April before she took office) that individual doctors should have the right to opt out of the European Working Time Directive that caps their working week at 48 hours.[1]

In the future there will be fewer surgical posts, Marx points out, and those who "really want to do surgery will make the time." Trainees will, she says, practise their surgical knots in their own hours and come in at weekends to see interesting operations. To prevent them is analogous, she says, to telling a professional violinist to stop practising.

Instead her focus is on the quality of surgical training and freeing-up trainees from delivering a service. "We know from our studies that trainees are really unhappy with their training in their early years, and the reason for that is that they are not being looked after— they are just doing service work," she says. "We don't know if you can be trained in 48 hours [a week], but I suspect that if you did nothing but train then you probably could."

Marx is keen to work with Health Education England on a curriculum and training pilot that allows trainees to focus on training as opposed to delivering a service.

Changing attitudes

Marx is proud of the college's recent report, *Good Surgical Practice* 2014 with its emphasis on professionalism, behaviours, and attitudes.[2] The report emphasises the importance of collaboration and shared decision making. Are these traditional surgical attributes I ask? "They will be in the future."

She is also keen on doctors taking responsibility for leadership and professionalism, which she sees as critical for improving quality of care. "What is great is when people are enabling, altruistic, collaborative within their teams and with the patients they listen to."

Marx supports the publishing of surgical outcomes but says that there is a limit to a surgeon's responsibility. She believes that quality and safety will be improved by doctors moving away from the "them and us" attitude to management and accepting that everything they do is part of management and moving the patient forward. "If you look at the big health organisations in the US, they are all run by doctors."

However far she moves on professionalism and safety, Marx's tenure will inevitably be judged, at least in part, by whether she succeeds in encouraging more women to become surgeons.

"We have good research that shows women just don't think they fit in surgery. "Part of this," she says cautiously, "is that they don't see enough women, dare I say it, at the top of their profession that are normal rather than superwomen."

Luisa Dillner is head of BMJ research and development, *The BMJ*, London, UK **ldillner@bmj.com**

Cite this as: *BMJ* 2015;350:h462