

# An end to the **STATIN** debate?

The effective use of statin therapy to reduce low-density lipoprotein (LDL) cholesterol by 2mmol/L can reduce a patient's risk of a major vascular event by almost 50%. This was one of the main findings of a new review on the safety and efficacy of statin therapy, published in *The Lancet*.

## Review author, Prof Rory Collins of

the Clinical Trial Service Unit based at University of Oxford (UK), and colleagues warn that the benefits of statin therapy have been underestimated, and the harms exaggerated, because of a failure to properly evaluate evidence from randomised controlled trials (RCTs), and to acknowledge the limitations of other types of studies. According to the authors, the aim of their review is to 'help doctors, patients and the public make informed decisions about the use of statins'.

"Our review shows that the numbers of people who avoid heart attacks and strokes by taking statin therapy are much larger than the numbers who have side effects. In addition, whereas most of the side effects can be reversed with no residual effects by stopping the statin, the effects of a heart attack or stroke not being prevented are irreversible and can be devastating.

"Consequently there is a serious cost to public health from making misleading claims about high side effect rates that inappropriately dissuade people from taking statin therapy despite the proven benefits," said Prof Collins.

According to Prof Liam Smeeth of the London School of Hygiene & Tropical Medicine (UK) and co-author, the best available scientific evidence tells us that statins are effective, safe drugs that have a crucial role in helping prevent cardiovascular disease (CVD), the leading cause of morbidity and mortality worldwide.

## EVALUATING THE EVIDENCE

The safety and efficacy of statin therapy has been the focus of research for over 30 years, generating a large amount of data. Research include randomised controlled trials (RCTs), meta-analyses and observational studies.

RCTs are a robust and well recognised way of determining the effect of treatments. In RCTs, patients are randomly divided into two or more groups. For example, one group is given a drug and the other group is given placebo. Researchers then compare the rates

of health outcomes between these groups. Randomly allocating patients means that any difference in these rates can generally be attributed to the treatment itself. In addition, by 'blinding' patients and their doctors as to whether they are taking the drug being studied or a placebo, eliminates bias in the assessment of health outcomes between the different treatment groups. In short, RCTs determine cause and effect.

Observational studies on the other hand, use information obtained from databases to generate hypotheses about associations between the use of drugs and health outcomes. Observational studies therefore compare the health outcomes of people who have been given a particular



## COMMENT BY PROF JAMES KER

Used appropriately, modern medical therapies have the potential to prevent a large proportion of the burden of cardiovascular disease. However, their appropriate use relies on the availability of robust data on safety and efficacy, as well as on a sound understanding of the interpretation and application of such evidence.

This new study explains how to understand the different methods of research on statin therapy and it discusses the strength and weaknesses of each method with examples from the statin trials.

### SOME OF THE PROVEN BENEFITS OF STATIN THERAPY

- 1 Evidence from many randomised trials shows that for each 1mmol/l reduction of LDL-cholesterol, is associated with a relative reduction of about 25% in the rate of major CV events.
- 2 Reducing LDL-cholesterol by 2mmol/l produces a relative risk reduction in major cardiovascular events by about 45%.

### SOME OF THE ADVERSE EFFECTS OF STATINS

- 1 Treating 10 000 patients could be associated with five cases of haemorrhagic strokes.

2 The harmful effects of statin therapy can usually be reversed by stopping it whereas the harmful effects of coronary heart disease and strokes that occur because statin therapy has not been used can be devastating.

### CONCLUSION

There is serious cost to public health of making misleading claims about the misgivings of the safety of statins and about the underestimated efficacy. Cholesterol-lowering therapy, including statin therapy, is substantially underused by people with a high risk to develop CV disease.

➤ treatment by their doctors as part of routine care, and people who have not been given the treatment.

Doctors give treatments to selected patients. The health of these patients may be very different to the health of people who are not given it. These differences in the underlying risks of the different groups of patients are hard to predict, and it is not possible to know that they have been allowed for completely in the analyses.

**25%**  
proportional  
reduction in major  
vascular events  
with each 1mmol/L  
reduction in LDL  
cholesterol

In addition, patients prescribed a drug in routine care know that they are getting it, and their doctors may have warned them that the drug may cause problems. Consequently, the patients may be more likely to attribute health outcomes (particularly symptoms that are subjective, e.g. muscle aching) to the drug, whereas people who are not taking the drug would not do so.

Therefore, argue the authors, although observational studies may be able to detect large increases in health outcomes that would usually be rare, they are not able to produce reliable evidence about the effects of drug treatments when the health outcomes are common or the effects are not large.

Meta-analyses bring together evidence from RCTs that have tested the same treatment and, by including data from a larger and more diverse set of patients, increase the reliability and generalisability of the results.

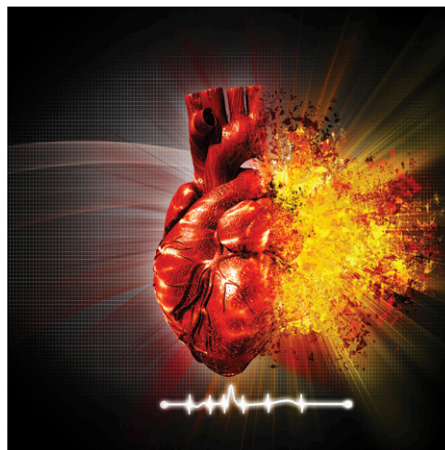
#### BENEFITS OF STATIN THERAPY

The authors reviewed the evidence and found the following:

- ⊕ Effective statin regimens reduce LDL cholesterol by more than 50% (e.g. at least 2mmol/L in individuals presenting with LDL cholesterol concentrations of  $\geq 4$ mmol/L).
- ⊕ Each 1mmol/L reduction in LDL cholesterol with statin therapy produces a proportional reduction of about 25% in the rate of major vascular events (coronary deaths, myocardial infarctions, strokes, and coronary revascularisations) during each year (after the first) that it continues

to be taken. Consequently, lowering LDL cholesterol by 2mmol/L reduces risk by about 45%.

- ⊕ Lowering LDL cholesterol by 2mmol/L with an effective statin regimen for about five years in 10 000 patients would typically prevent major vascular events in about 1000 (10%) patients at high risk of heart attacks and strokes (e.g. secondary prevention) and 500 (5%) patients at lower risk (e.g. primary prevention).
- ⊕ A statistically significant 12% proportional reduction in vascular mortality per mmol/L LDL cholesterol reduction. The reduction can mainly be attributed to a 20% proportional reduction in coronary deaths (with, as was seen for major vascular events, a greater proportional effect after the first year of treatment), along with an 8% reduction in other cardiac deaths.
- ⊕ Some observational studies claim that statin therapy might also reduce the risks of cancer and various other conditions (including respiratory diseases and infections, deep vein thrombosis, and post-operative atrial fibrillation). However, the evidence from randomised trials shows that these associations in observational studies do not reflect a causal effect of statin therapy. The authors therefore concluded there is not good evidence that statin therapy produces beneficial effects on other health outcomes (e.g. cancer, infections, respiratory disease, arrhythmias).



The authors recommend that intensive statin therapy should be focused on patients at higher risk of vascular events rather than just on those with high cholesterol concentrations. The reason for this is because the proportional reductions in rates of vascular events with statin therapy are related to the absolute reductions in LDL cholesterol that are achieved.

#### HARMS OF STATIN THERAPY

The authors found the following:

- ⊕ Evidence from some observational studies and randomised trials points

to a causal effect of statin therapy on myopathy, a rare condition involving muscle pain, tenderness or weakness accompanied by significant increases in blood creatine kinase concentrations. However, state the authors, the risk is low (approximately one extra case per 10 000 patients taking an effective statin regimen during each year of treatment).

Intensive statin  
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at higher risk of  
vascular events

- ⊕ In the SEARCH RCT, simvastatin 80mg daily produced a more than ten-fold higher rate (at least one case of myopathy per 1000 patients treated yearly) than 20mg daily (or 40mg daily in high risk patients, about one case per 10 000 yearly). High dose regimens are therefore no longer recommended routinely. The rates of reports of myopathy in regulatory databases are also higher with higher doses of atorvastatin, although such spontaneous reports may be biased and the absolute risks are still small even with the highest approved dose.
- ⊕ Randomised trials have also shown an increase risk of diabetes due to statin therapy (approximately 10 to 20 extra cases of diabetes developing per 10 000 treated patients per year). This excess of diabetes occurs mainly in people who are already at increased risk of developing diabetes, and its clinical significance is uncertain. In particular, although diabetes is associated with increased risk of vascular disease, statin therapy produces substantial reductions in vascular disease, noted the authors.
- ⊕ In addition, some observational studies suggest that statin therapy may be associated with an increased risk of haemorrhagic stroke. Randomised trials indicate that statin therapy may increase the risk of haemorrhagic stroke by about one-fifth. This corresponds to an increase of about five to 10 extra cases per 10 000 treated patients per year. In most circumstances, the reductions in ischaemic strokes produced by statin therapy are much bigger than the increases in haemorrhagic strokes, so the risk of stroke of any kind is reduced substantially.

## Average relative reduction in LDL cholesterol concentrations with different doses of statins

Daily dose	5mg	10mg	20mg	40mg	80mg
Pravastatin	15%	20%	24%	29%	33%
Simvastatin	23%	27%	32%	37%	42%
Atorvastatin	31%	37%	43%	49%	55%
Rosuvastatin	38%	43%	48%	53%	58%

Some studies have also found a link between statin therapy and increased rates of muscle pain and weakness. This has led to claims that as many as 20% of patients have 'statin intolerance', due to muscle pain and weakness. However, said the authors, evidence demonstrates that these claims are wrongly attributed to symptoms caused by the use of statin therapy. According to the authors, statin therapy rather causes an increase in symptomatic adverse events (e.g. muscle pain and weakness) in about 10 to 20 of 10 000 treated patients per year.

Claims that statin therapy might increase the risks of various other conditions (e.g. memory loss, cataracts, kidney injury, liver disease, sleep disturbance, aggression, suicidal behavioural, erectile disjunction and neuropathy) are also not accurate. Evidence from randomised trials shows that these associations in observational studies do not reflect a causal effect of statin therapy.

12%

proportional reduction in vascular mortality per 1mmol/L LDL cholesterol reduction

## EFFICACY OF DIFFERENT STATINS

The authors pointed out that different statins have different potencies. Newer agents such as atorvastatin and rosuvastatin are able to produce larger reductions in LDL cholesterol per mg of drug than older agents. Irrespective of the statin used, each doubling of the dose produces an extra reduction of about 6% points in LDL cholesterol.

According to the authors, the absolute benefits of using statin therapy depend on an individual's absolute risk of atherosclerotic events and the absolute reduction in LDL cholesterol that can be achieved. For example, five years of treatment with a statin regimen that lowers LDL cholesterol by 2mmol/L would be expected to prevent major vascular events in about 1000 (10%) higher risk patients per 10 000 treated and

in about 500 (5%) lower-risk patients per 10 000 treated.

## CONSEQUENCES OF MISLEADING CLAIMS

A study by the Picker Institute (UK) found that negative media coverage about the side effects of statins led increased reticence among the doctors to discuss and prescribe statins, and reduced compliance by the patients. This has negative impact on public health, said the authors.

As a result of these negative reports, often based on the inaccurate interpretation of RCT results, statin therapy is substantially underused by people at high risk of heart attacks and strokes.

In the 2016 PURE study, conducted in 22 countries, 66% of individuals aged 35–70 years with CVD were using statin therapy in high income countries, but only 27% in upper middle income countries and approximately 5% in lower income countries.

In addition, the SHARE study, involving patients from various European countries, found that only 42% of individuals aged at least 50 years with prior CVD were taking any form of statin therapy in 2013. There were large variations between different countries (e.g. 55%–56% in Belgium, Denmark or the Netherlands versus 27%–29% in Estonia or Slovenia).

In a cross-sectional study based on the Australian National Health Measures Survey in 2011–12, statin therapy was being taken by 56% of people aged 45–74 years who had pre-existing CVD and by 33% of those considered to have a high five year risk (>15%) of a primary CVD.

In the 2010 US Medical Expenditure Survey, researchers found that statin therapy was used by 58% of people aged 30–79 years with coronary artery disease and by 52% of those aged older than 40 years with diabetes.

Analyses of the Clinical Practice Research Datalink conducted in the UK in 2014–15, it was found that statin therapy had been started by only about 60% of patients who had recently had a first CV event and by only approximately 25% of patients in whom a 10-year CV risk of 20% or more had been recorded by their GP within the past month.

A Danish study found that negative statin-related news stories were followed by increases of about 10% in patients stopping taking statins.

A follow up study after the broadcasting of an Australian television programme about the possible side effects of statins showed a reduction in the number of prescriptions of statin therapy for patients at elevated risk of heart attacks and strokes. The programme was withdrawn after it was found that it misinterpreted the evidence about statins, however, the researchers estimated that about 60 000 fewer Australians had statins dispensed than predicted from previous rates and that, if those patients continue to avoid statin therapy during the next five years, between 1500 and 3000 potentially fatal heart attacks and strokes will occur that could have been avoided.

As a result of these negative reports, often based on the inaccurate interpretation of RCT results, statin therapy is substantially underused by people at high risk of heart attacks and strokes.

An analyses of prescription data from the UK Clinical Practice Research Datalink following the publication of an article claiming that statins cause side-effects in approximately 20% of patients, found that there was a proportional increase of about 10% in patients stopping statin therapy for secondary and primary. According to the researchers more than 200 000 UK patients stopped taking their statin therapy, which they estimate will result in between 2000 and 6000 CV events occurring during the subsequent decade that could have been avoided.

The authors concluded that greater caution is warranted when making claims about possible drug side effects, because it can lead to patients at high risk of heart attacks, strokes, and related deaths, and their doctors from using statin therapy despite the proven benefits, resulting in deaths that could have been avoided.

Source: *The Lancet*

## REFERENCE:

Collins R *et al.* Interpretation of the evidence for the efficacy and safety of statin therapy. *The Lancet*. 2016. [58](#)

Multiple choice questions

# An end to the **STATIN** debate?

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- 1** Effective statin regimens reduce LDL cholesterol by more than \_\_% (e.g. at least 2mmol/L in individuals presenting with LDL cholesterol concentrations of  $\geq$ 4mmol/L).
- a. 40%  A  
 b. 60%  B  
 c. 50%  C  
 d. 70%  D
- 2** The authors recommend that intensive statin therapy should be focused on patients at:
- a. Higher risk of vascular events.  A  
 b. Those with high cholesterol concentrations.  B  
 c. Higher risk of vascular events rather than just on those with high cholesterol concentrations.  C
- 3** Lowering LDL cholesterol by 2mmol/L with an effective statin regimen for about five years in 10 000 patients would typically prevent major vascular events in about \_\_% patients at high risk of heart attacks and strokes.
- a. 12%  A  
 b. 20%  B  
 c. 30%  C  
 d. 10%  D
- 4** Lowering LDL cholesterol by 2mmol/L reduces risk major vascular events by about \_\_%.
- a. 25%  A  
 b. 30%  B  
 c. 45%  C  
 d. 20%  D
- 5** Statin therapy might also reduce the risks of cancer and various other conditions (including respiratory diseases and infections, deep vein thrombosis, and post-operative atrial fibrillation).
- a. True  A  
 b. False  B
- 6** The risk of myopathy is low (approximately one extra case per 10 000 patients taking an effective statin regimen during each year of treatment).
- a. True  A  
 b. False  B
- 7** Some observational studies suggest that statin therapy may be associated with:
- a. An increased risk of haemorrhagic stroke.  A  
 b. A reduced risk in ischaemic strokes.  B  
 c. An overall reduction of risk.  C  
 d. All of the above.  D
- 8** Randomised trials have also shown an increase risk of diabetes due to statin therapy (approximately 10 to 20 extra cases of diabetes developing per 10 000 treated patients per year). This excess of diabetes occurs mainly in people who:
- a. Are already at increased risk of developing diabetes.  A  
 b. Are overweight.  B  
 c. Are over the age of 65.  C
- 9** Evidence demonstrates that claims that statin therapy increase rates of muscle pain and weakness are wrongly attributed to symptoms caused by the use of statin therapy.
- a. True  A  
 b. False  B
- 10** According to the authors, inaccurate media reports about the side effects of statins, led to an increase in the number of patients who stop taking their medication, which can result in deaths that could have been avoided.
- a. True  A  
 b. False  B

This is to state that I have participated in the CPD-approved programme and that these are my own answers.

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