LETTERS

ADVERSE EFFECTS OF STATINS

(Mis)interpreting studies on the adverse effects of statins

Our study “Discontinuation of statins in routine care settings”¹ has been cited in recent discussions in The BMJ on statin intolerance.²³⁴ Some of these reports misinterpreted our study.

Our study sought to investigate the “real world” experience of patients who developed symptoms that they, or their healthcare providers, thought might have been caused by statins. Using natural language processing to analyse more than 100,000 patient records, we found that statin re-challenge after a presumed statin related event led in more than 90% of cases to patients taking a statin long term. We concluded “that many of the statin-related events may have other causes, are tolerable, or may be statin specific.”² Our findings were later confirmed in another large study.³ Taken together, we stand by our report, including our note of the study’s limitations.

The goal of our study was never to establish the rate of adverse reactions caused by statins, which would be impossible with the tools that we used. Our paper never used the term “adverse reactions to statins,” referring instead to “statin-related events,” defined as “clinical events or symptoms believed to have been caused by statins.” Implicit in this definition is the recognition that the causative association between each identified event and statin use was unknown.

Both randomised clinical trials and observational studies have a limited ability to estimate the rate of true adverse reactions in actual patient care. Accurate identification of adverse reactions to statins will probably require a better understanding of the mechanisms involved, thus allowing development of more precise tests. Nevertheless, careful interpretation of all available data can help guide prudent clinical management and avoid the dangerous prospect of patients with serious cardiovascular risk never undergoing statin re-challenge when they may have been able to tolerate the drug.

Huabing Zhang associate chief physician, Key Laboratory of Endocrinology of Ministry of Health, Department of Endocrinology, Peking Union Medical College Hospital, Beijing 100730, China
Jorge Plutzky director, the vascular disease prevention program
Alexander Turchin associate professor of medicine, Brigham and Women’s Hospital, Boston, MA 02115, USA aturchin@partners.org

Competing interests None declared.

Full response at: www.bmj.com/content/348/bmj.g3306/rt.scroll/699864.


Cite this as: BMJ 2014;348:g3652

True incidence of statin side effects must be established

One key area of the debate about widening the use of statins is the discordance between rates of side effects of statins in clinical trials and in clinical practice.¹ In clinical trials, the incidence of side effects from statins is low and similar in the intervention and placebo groups.² By contrast, observational studies using primary care databases report a much higher rate of potentially serious side effects (such as myopathy and renal failure) in people taking statins.³⁴ Even these rates derived from clinical records may underestimate the true incidence of side effects in people taking statins, because not all patients with side effects inform their doctor and not all doctors enter a relevant diagnostic code in the patient’s electronic medical record.

Many GPs will be familiar with patients who report side effects after starting statins. These side effects are often severe enough for patients to stop taking the drug. Of course, these side effects could be coincidental or psychosomatic and nothing to do with the drug. It is also possible that previous clinical trials (most of which were carried out many years ago) under-recorded the side effects of statins.

Statins are highly effective in lowering cardiovascular risk and improving clinical outcomes.³ However, we urgently need to establish the true incidence of the side effects of statins if doctors and patients are to be encouraged to increase the use of these drugs, particularly in people with lower levels of cardiovascular risk.

Azeem Majeed professor of primary care, Imperial College London, London W6 8RP, UK a.majeed@imperial.ac.uk
Mariam Molokhia reader in epidemiology and primary care, King’s College London, London, UK

Competing interests None declared.


Cite this as: BMJ 2014;348:g3650.

Muscular adverse effects are common with statins

The 2011 Cochrane review of statins for the primary prevention of cardiovascular disease reported a risk ratio of 1.03 for muscle pain—3% more patients developed muscle pain on the drug than on placebo.¹ However, industry funded randomised trials are notoriously unreliable when it comes to the harms of drugs.² The results of a publicly funded randomised trial from 2012 on the impact of statins on energy and exertional fatigue could be interpreted as 20% of men and 40% of women experiencing reduced energy or increased exertional fatigue.³ I therefore wonder why Rory Collins has pressured the BMJ in a most unacademic way for having published a paper based on a cohort study that reported a similar incidence of harms.²²³ He has even called for a retraction of the paper, just like drug companies often...
OPEN LETTER TO THE GOVERNMENT

Government must draw up law on tobacco plain packaging soon

Smoking related disease remains the main cause of preventable deaths in the UK, killing more than 100 000 people each year. Most smokers start in childhood, and exposure to tobacco marketing is known to increase this risk.¹ To protect public health, particularly the health of children at risk of becoming smokers, it is therefore necessary and logical to end the marketing of cigarettes and tobacco products through packaging.²

Standardised tobacco packaging includes large picture and text warnings about the health consequences of smoking, as well as clear advice about where to get help to quit. Colourful branding elements that mislead and distract from health messages are removed.¹ Cyril Chantler’s independent review found good evidence to support this measure,¹ ³ and rejected misleading tobacco industry opposition.⁴ Chantler found no reason why standardised packaging would increase the level of illicit trade in tobacco. Key security features on existing packaging will be retained on standardised packs, including number codes and covert anti-counterfeit marks.

Parliament voted overwhelmingly to support the introduction of standardised packaging, and the public health minister announced in parliament that she hoped to publish the draft regulations for consultation before the end of April.¹ Nearly two months have passed and this has still not happened.

The government has committed to a six week public consultation period after the draft regulations are published, and it will also need to notify the EU of the draft regulations, under Directive 98/34/EC. This process can take up to six months. There is a relatively short time left for the government to produce the draft regulations if they are to be voted on by parliament before the general election. We therefore ask you to confirm that they will be published in the next few weeks.

Nicholas S Hopkinson consultant chest physician and chair British Thoracic Society chronic obstructive pulmonary disease specialist advisory group, National Heart and Lung Institute, Imperial College, London SW3 6NP, UK n.hopkinson@ic.ac.uk

John Britton professor of epidemiology, University of Nottingham, Nottingham, UK

Anna Gilmore professor of public health, University of Bath, Bath, UK

John Moxham professor of respiratory medicine, King’s College London, London, UK

John R Ashton president, UK Faculty of Public Health, London, UK

On behalf of 584 others

Competing interests: None declared.


Cite this as: BMJ 2014;348:g3779

COLORECTAL CANCER: A CAUTIONARY TALE

Assess current practice before introducing “next new thing”

The story of colorectal cancer metastasectomy does not end with Treasure and colleagues’ fascinating tale.¹ A recent randomised trial looked at the usefulness of positron emission tomography-computed tomography (PET-CT) for identifying suitable candidates for colorectal cancer liver metastasis surgery.² Unlike an earlier trial, which had profound weaknesses, it found no evidence of benefit from PET-CT.³ ⁴ Both trials investigated whether patients could be spared unnecessary surgery because of unacceptably metastatic spread identified by PET-CT.

In Germany we intend to conduct a more thorough investigation into the usefulness of PET-CT in recurrent colorectal cancer. Treasure and colleagues highlight a serious problem we have encountered in planning future research: how wise is it to implement a new intervention (PET-CT in this case) when, on close investigation, the value of the current “standard of care” is doubtful? When looking at this case a remarkable understanding of “medical progress” is revealed. Firstly, intensive carcinoembryonic antigen (or CT) screening in colorectal cancer follow-up is used to detect recurrence as early as possible, then an aggressive surgical approach is pursued, and afterwards additional advanced diagnostic imaging (PET-CT) is used to exclude patients from surgery again.

Non-publication is but one variation of wasteful research. Another less obvious one is conducting studies (such as myriads of “diagnostic” studies and case series, particularly in surgery) that are in serious danger of being misleading. We may have to...
think about the extent of our “addiction to technology adoption,” and instead turn our attention to current practices before the “next new thing” is introduced.

Philipp Storz-Pfennig officer for technology assessment, GKV-Spitzenverband (German National Association of Statutory Health Insurance Funds), D-10117 Berlin, Germany

Philipp.Storz@gkv-spitzenverband.de

Competing interests: None declared.

Full response at: www.bmj.com/content/348/bmj.g3111/r/699032

1 Godlee F. Colorectal cancer: a cautionary tale [Editor’s Choice]. BMJ 2014;348:g3111. (17 May)


5 Bryan’s, Mitton C, Donaldson C. Breaking the addiction to technology adoption. Health Ecan 2014;23:379-83.

Cite this as: BMJ 2014;348:g3729

HPV VACCINATION

Boys in the UK should be offered HPV vaccine

Wise reported that of the girls and young women who were offered vaccination against human papillomavirus (HPV) only half the women not in education, employment, or training were included in the offer.

Much more concerning is the fact that oropharyngeal cancer driven by HPV has the fastest rising incidence of any cancer, yet no boys in the United Kingdom are offered vaccination.

We have written to express our concern at the UK policy with regard to vaccination against HPV, which actively discriminates against men and boys, and are disappointed by the lack of response. A reply to similar concerns expressed in the Houses of Parliament demonstrates the resistance to offering gender neutral vaccination is based, without evidence, on the idea that this is a problem that only affects men who have sex with men.

An abundance of evidence demonstrates the involvement of HPV 16 and 18 in the dramatic increase in incidence of oropharyngeal carcinoma. Although this is commoner in younger, more active, members of the population and is easier to treat in non-smokers, the burden on survivors is considerable. The disease remains more common in men and boys.

Australia agreed to vaccinate boys with the quadrivalent vaccine at ages 12-13 years with a catch up at 14-15 during 2014. The UK continues to exclude boys from this effective preventive programme for malignant disease.

There is no scientific argument against the clinical benefit of sex neutral vaccination at 12-13 years. It is purely financial. We think that the devastating effects and cost in terms of both treatment and care for the younger working age survivors have been grossly underestimated.

Australia has clearly come to the conclusion that this important preventive initiative can be made cost effectively. We must also recognise that the potential for deliberate sex discrimination has to be avoided.

This decision must now be revisited at the earliest opportunity.

David Mitchell member david.mitchell@mdyorks.nhs.uk

Riccardo Audisio member Garth Cruickshank member

Stephen Cannon member Talvinder Gill member

Andrew Hayes member Sean Kehoe member

Jim McGuigan member Barry Powell member

Nick Price member

Nicholas Roland member

Lynda Wyld member, Royal College of Surgeons of England, London WC2A 3PE, UK

On behalf of the Cancer Services Committee

Competing interests: None declared.

Full response at: www.bmj.com/content/348/bmj.g2190/r/698445

1 Wise J. Young women most at risk are least likely to be offered HPV vaccine. BMJ 2014;348:g2190. (18 March)

2 UK parliament. Daily Hansard—debate 13 Jan 2014. www.publications.parliament.uk/pa/cm201314/cmhansrd/cm140113/debtext/140113-0004. html#1401133300057


Cite this as: BMJ 2015;348:g3762

WHO PAYS THIS DOCTOR?

What about a publicly available list held by the GMC?”

The imbalance in the relationship between doctor and patient means that knowledge of a doctor’s financial interests will never be a panacea for resolving all biases and prejudices in medicine. However, a register like whopaysthisdoctor.org is not just for patients, but for doctors also.

As doctors, we often rely on the views of key opinion leaders for the clinical knowledge we acquire and the decisions that we make. Whether information comes from journal articles, editorials, educational events, or published guidance, it is essential that we have a good understanding of whose lead we are following, and whether those involved have any affiliation with the treatment that they recommend.

Inconsistencies in declarations often make it difficult to ascertain a doctor’s interests, particularly at conferences and educational events, where the culture of declaration is not well embedded. A single, compulsory, publicly available list held by the General Medical Council would make such a process simple and reliable. It would also be convenient for doctors, who could make only one declaration each year, rather than every time they publish.

Martin Brunet general practitioner, Binscombe Medical Centre, Godalming GU7 3PR, UK

Competing interests: I have received income from publishers, including Pulse, Prescriber, and the Guardian, for writing and speaking. I played a small part in setting up the website whopaysthisdoctor.org and my full declaration can be found there.

1 McCartney M. Who pays this doctor? It’s time patients knew. BMJ 2014;348:g3039. (6 May.)

Cite this as: BMJ 2014;348:g3646

Who pays for this conference? Time patients and doctors knew

McCartney notes that patients do not know whether their doctors are chosen key opinion leaders who are paid by a drug company to increase prescribing of a drug, or whether their doctors’ travel to international conferences was paid for by the drug company that makes the product that is being recommended to them.

Because of the potential effect on speakers and audience, some information disseminated in scientific meetings might be biased, and prescribing practices might be influenced. Patients should know not only who pays for medical conferences, but for doctors also.

Health authorities should set up a public central registry of competing interests for scientific societies or individual organisers where declarations regarding medical conferences and invited speakers can be listed. Conflicts of interest should be published in the online and printed programmes for each conference.

Through these simple measures, lay people and audience members would be aware of several points.
Canterbury tale

under New Zealand’s Official Information Act about funding sources. The King’s Fund did not reveal these, and the editorial seems to have taken the fund’s findings as those of an independent evaluation. It now transpires that the Canterbury District Health Board paid £96,000 (NZ$186,000; €118,400; $161,230) for the report and, presumably, commissioned the King’s Fund to do it. By contrast, evaluations of four other New Zealand integration sites, more revealing in terms of the “progress” and challenges involved, were undertaken independently through the New Zealand Health Research Council.

The BMJ has led on championing transparency. Trials published in the journal are subject to considerable scrutiny. We believe readers expect similar scrutiny when it comes to studies on which editorials are commissioned and suggest that a protocol for this is developed. This should then be adopted by the International Committee of Medical Journal Editors. The BMJ has an opportunity, perhaps an obligation, to lead the way here. The King’s Fund may have reported some useful lessons for those interested in health system integration but, unfortunately, did not acknowledge among other less positive indicators the level of ongoing unmet need for healthcare in Canterbury.

Rather, as in the case of the drug industry, notorious for selective reporting of clinical trials, we believe that public perception has been manipulated. A transparency protocol for reports such as this and associated editorials would reduce this possibility.

Robin Gauld professor of health policy, Centre for Health Systems, Department of Preventive and Social Medicine, University of Otago, PO Box 56, Dunedin 9054, New Zealand robin.gauld@otago.ac.nz

Antony Raymont independent health services researcher, Milford, Auckland, New Zealand

Philip F Bagshaw chair, Canterbury Charity Hospital Trust, PO Box 20409, Christchurch, New Zealand

M Gary Nicholas emeritus professor Christopher M Frampton associate professor of biostatistics, Department of Medicine, PO Box 4 345, University of Otago, Christchurch, New Zealand

Competing interests: None declared.

Full response at: www.bmj.com/content/348/bmj.g3778

Cite this as: BMJ 2014;348:g3778

CONFLICTS OF INTEREST

King’s Fund reply

I have a high regard for Robin Gauld, and the essential point that he and his colleagues make is correct—all sources of funding should be transparently declared.1

But I resent the innuendo that lards their letter. It falsely states that the board, not the fund, wrote the report. It makes unwarranted accusations of manipulation, along with overblown comparisons of selective reporting by the drug industry. And they glibly relate that they found this out through a Freedom of Information request, implying a conspiracy. They could simply have picked up the phone and asked. We would have told them. We have nothing to hide here. In all presentations in the UK and New Zealand we made clear that the Canterbury District Health Board commissioned this work. It might be seen to be implicit in the acknowledgments, but it should definitely have been explicit. An unfortunate act of omission does not, however, spell conspiracy. Nor does it involve one. The King’s Fund retained full editorial control throughout, as stated in an agreement that the study was to be warts and all. The fund, not the board, wrote the report, and Gauld and colleagues’ view that it is “overly positive” is a matter of judgment and debate around the available evidence.

As for unmet need, Canterbury is clearly meeting more clinical need than it was, and I would be surprised if Gauld and colleagues could name any health system, including their own, with no unmet needs. Their core point is valid. I am slightly surprised that it takes five academics to make it.

Nicholas Timmins senior fellow, King’s Fund, London W1G OAN, UK nicholas.timmins@gmail.com

Competing interests: None, other than that I work for the King’s Fund on contract.


Cite this as: BMJ 2014;348:g3775

Cite this as: BMJ 2014;348:g3748


Competing interests: None declared.

Full response at: www.bmj.com/content/348/bmj.g3039/rr/698485.

Cite this as: BMJ 2014;348:g3039


