

Electronic records may threaten blinding in statin trials

Records of changes in cholesterol can show whether patients are receiving intervention or not—biasing trials to make statins look more beneficial than they really are, argues **Paul v Nguyen**

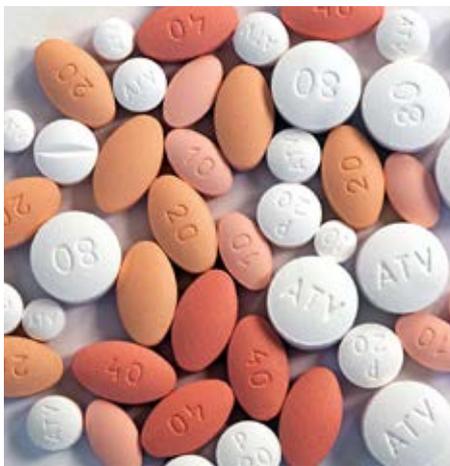
Newly released US guidelines on cholesterol that promote more use of statins¹ have been criticised as being over-reaching² and biased.³ These guidelines are based on a meta-analysis of individual data from many randomised trials.⁴ But a previously overlooked problem may also have inflated the perceived benefits of statins: a lack of concealment of patient allocation.

In randomised controlled trials of the clinical efficacy of cardiovascular drugs in general—and statins in particular—a key control measure is the double blinding of patients, caregivers, and especially investigators and outcome assessors. A lack of blinding may significantly bias results in favour of the drug under study,⁵ particularly if clinical efficacy is based mostly on “soft outcomes” (those influenced by judgment or perception), such as the diagnosis of angina, or decisions on admission to hospital or on cardiac catheterisation or revascularisation.⁶

“Unblinding” can occur inadvertently in clinical trials when patient data are available in electronic health records. For example (and it has happened to me more than once), records could show a sustained drop in a participant’s low density lipoprotein cholesterol (LDLC) concentration, from 3.5 mmol/L to 1.5 mmol/L, two months into a double blind trial to test statin against placebo—indicating that the patient had been allocated to the active drug group.

Hence unblinding may occur when doctors, whether working in the same health centre or at another medical institution where records are shared and consulted, check patients’ records to treat a concomitant medical or cardiovascular condition. They may guess patients’ allocation and, inadvertently, share it with them. The same situation applies whenever the investigator is both a caregiver and an evaluator of outcomes. And among patients, the psychological effect of knowing whether or not they are receiving a superior treatment may influence how they report symptoms to their caregivers.⁶

More important biases may occur when, for example, a vague shortness of breath or an unconvincing chest pain reported during a follow-up visit by a patient with a low LDLC (and thus thought to be in the active drug arm) is downplayed as a non-cardiac problem and the



patient is simply reassured. In such a case, a diagnosis of an atypical angina may be delayed. Conversely, in the same symptomatic patient, but one with a high LDLC (and thus thought to be allocated to the placebo arm), unstable angina may be more readily diagnosed and the patient may be admitted to hospital and subjected to a coronary angiography—and then, if needed (in line with various subjective and objective parameters), subjected to angioplasty and most often to stenting (revascularisation). The three latter procedures are considered “soft” subjective outcomes, because they are not disease endpoints in themselves but medical decisions based on the attending cardiologist’s attitude.

Unfortunately, statin trialists often use composite endpoints comprising hard, robust outcomes (fatal myocardial infarction, cardiovascular death, fatal stroke, all cause mortality) mixed with softer, more subjective ones (diagnosis of unstable angina, admission to hospital, revascularisation). This heterogeneity reduces validity⁷ and has been identified, for instance, in the primary prevention JUPITER trial, as well as in many other trials that showed inexplicable discrepancies between some cardiac endpoints and cardiac mortality.⁸

The ascertainment bias, arising from consciously or unconsciously stacking several “soft” outcomes in the placebo arm, may help composite endpoints to reach statistical significance misleadingly, even when “hard” outcomes by themselves do not.⁹ For instance, in the JUPITER trial the only significant difference

among women in any of the five primary endpoint components was the claimed 73% reduction in revascularisations in the statin arm.¹⁰

Can the bias be quantified? It depends on the outcomes. Possibly yes, for already controversial decision outcomes such as revascularisations¹²—but this would involve painstaking objective and blinded review of the angiographic data, if made available, of each individual case. And the answer is probably no for subjective outcomes, such as diagnosis of angina or decisions about admission to hospital or catheterisation.

Is this problem solvable for ongoing and future studies of lipid lowering agents? There may be two solutions, neither one completely satisfactory. The first would be to enforce strict double blinding (among patients, caregivers, and outcome assessors) of lipid status for the duration of the study. This would mean preventing trial participants from undergoing lipid tests, which may be difficult to implement in a large scale trial and may be criticised for not representing current practice where current lipid status is an important part of cardiovascular risk assessment.¹

The second would be to accept that unblinding is inevitable and design the trial endpoints to minimise the risk of distorting the results. The problem would then remain in its entirety, and the only outcome free of such bias would be death and, hopefully, confirmed fatal cardiovascular events. However, most deaths, especially in cohorts with low cardiovascular risk, may be non-cardiovascular and therefore not amenable to statin prevention.

The proliferation of electronic notes may increase the likelihood of unblinding in efficacy trials of lipid lowering agents by revealing a lipid profile, particularly LDLC, that is unmistakably lower in the treatment arm. This may bias subjective outcomes enough to reach statistical significance, making the drug under study look more efficacious than it actually is.

Paul v Nguyen is internal medicine specialist, Centre Hospitalier Universitaire de Montréal, 3840 St-Urbain, Montreal, Quebec, Canada QCH2W 1T8
pnyuyen920@aol.com

Competing interests: None declared.

Provenance and peer review: Not commissioned; externally peer reviewed.

References are in the version on thebmj.com.

I thank Pierre Biron, Michel de Lorgeril, and Jeanne Lenzer for their help in preparing this article.

Cite this as: *BMJ* 2014;349:g5239

NO HOLDS BARRED Margaret McCartney

Fat doctors are patients too

Belgium's new health minister, Maggie De Block, is a former GP. She also reportedly weighs 20 stone (127 kg), prompting critics to claim she is unsuitable to manage a portfolio that includes reducing obesity.

Recently, England's chief medical officer, Sally Davies, said that she was "perpetually surprised" at how many NHS staff were overweight. "How are they to have the impact on patients if they are not thinking about it for themselves?" she asked.¹ Meanwhile, Simon Stevens, chief executive of NHS England, has told staff to join gyms and weight loss clubs, to "fight against obesity."²

The message for doctors is clear: don't be fat. But obesity is complex. It is closely related to mental distress,³ including depression.⁴ Unlike excessive drinking, smoking, drug misuse, or unprotected sex, this "unhealthy" state is hard to hide.

Overweight and pregnant women talk of stigma and of "humiliation"



Those of us who have gained, lost, gained, lost, and gained weight again are only too aware of our failings

thebmj.com/blog

● Fat—the word that dare not speak its name in *The BMJ*?
<http://bmj.co/1tpLkp9>

Twitter

● @mgmtmccartney

during antenatal care.⁵ Patients feel shame and a reluctance to talk about their weight, despite a strong sense of personal responsibility.⁶ And almost a quarter of nurses in a North American study said that they were repulsed by caring for obese patients.⁷

Healthcare staff are patients too. We professionals, who deal daily with the consequences of obesity, have weight problems ourselves; knowledge doesn't make us immune. Much has been made of US studies purporting to show that patients trust fat doctors' advice less: but these were theoretical studies⁸ that did not examine patients in long term relationships with their own GPs.

Shift working is a risk factor for obesity,⁹ and less than a third of NHS doctors working them manage regular meals.¹⁰ Meanwhile, fast food franchises selling energy dense foods have gained a firm foothold in NHS hospitals.¹¹

Weight loss interventions in primary care yield clinically insignificant reductions in weight.¹² Of people invited to typical non-NHS weight loss programmes, only 1% have sustained their goal weight after five years.¹³

It would be better to concentrate on healthy work environments. The NHS should promote the health benefits of cycling, by committing to having most employees cycle to work, promoting safe cycle lanes, and ensuring bike storage and shower facilities.¹⁴

We should not assume that fat doctors are bad doctors or are "not thinking about it." Those of us who have gained, lost, gained, lost, and gained weight again are only too aware of our failings. The medical profession should be tolerant of these—the same problems that our other patients face.

Margaret McCartney is a GP, Glasgow. Competing interests and references are in the version on thebmj.com.

Cite this as: *BMJ* 2014;349:g6464

● **PRACTICE**, p 32

BMJ BLOG OF THE WEEK Samir Dawlatly

Silencing complaints will not stop a GP workforce crisis

Dear Department of Health and NHS England

It seems clear that you, the medical fraternity, as well as the mass media agree that there is a recruitment and retention crisis in general practice in England. What is also clear is that we have differing opinions on the reasons this crisis has arisen.

While doctors and some of the organisations that represent us are open about working conditions in the hope that they can be improved, it appears that you are intent on sticking to the same, seemingly rehearsed, lines. Recently, the Conservative health minister Lord Howe warned GPs to stop complaining about their work conditions, so that they did not cause a workforce crisis. Similar noises were heard from NHS England at the recent Royal College of General Practitioners Annual Conference.

Whether the audience is a room full of GPs, medical students, or a national newspaper, the message seems to be: "The reason for the GP recruitment crisis is that GPs complain so loudly about their conditions, putting off medical students and junior doctors—if they didn't complain so much we could recruit more GPs."

Even if that was true, it would only solve half the problem. If all GPs swore a solemn oath to never utter how difficult their job is, it may, just may, possibly, lead to more junior doctors choosing general practice as a specialty. But even if recruitment to a sugar coated profession was possible, keeping quiet about any issues would not help with the retention issues of GPs taking early retirement, emigrating, or changing profession. And what's more, many medical students get a chance to see for themselves what general practice is like

Not complaining about problems doesn't make problems go away

firsthand as part of undergraduate or postgraduate training.

Not complaining about problems doesn't make problems go away. If I buy my children shoes in haste that don't really fit them, and they then complain about the pain they are in, the solution to the situation is not to tell them to stop complaining about their discomfort; that won't solve the problem.

Raising issues demonstrates an integrity and willingness to tackle concerns that compromise patient care and/or doctor wellbeing. So instead of flogging the profession in the hope that it will boost morale, it may be worth listening to GPs.

For a start, why not recognise and deal with the huge amount of over-

Samir Dawlatly is a GP partner at Jiggins Lane Surgery in Birmingham



regulation we face: the Quality and Outcomes Framework, the Care Quality Commission, clinical commissioning group schemes, traffic light ratings on cancer referrals, and the family and friends tests, to name a few. It would also help to acknowledge that GPs are facing rising demand from a health anxious, risk averse, increasingly complicated, and older population, where more healthcare is expected to take place outside of the hospital setting.

Surely the best advert for general practice would be general practitioners who felt valued? Whether you heed this advice depends, of course, on whether your respective organisations want a vibrant, resilient, functional, and efficient general practice workforce as the foundation of a centrally funded national health service.

● **Read this blog in full and other blogs at thebmj.com/blogs**