Submissions to Panel

These submissions were received by the panel. The chair of the panel invited each submitter to send the submission as a rapid responses to the original article or the editorial about the panel's establishment in the BMJ, but most did not do so, preferring to have their submissions published at the time the panel reported. The submissions have been subject to normal legal pre-publication checking and some statements have been redacted for legal reasons (indicated by a three dot ellipsis)*

** Scott Grundy (submission 8) did send a rapid response arguing the points in the paper by Abramson et al: http://www.bmj.com/content/347/bmj.f6123/rr/700794*
**Peter Sever(submission 7) sent his submission as a rapid response*
http://www.bmj.com/content/348/bmj.g3306/rr/700606

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From: "Gersh, Bernard J., M.B., Ch.B., D.Phil." <Gersh.Bernard@mayo.edu>
To: "iona.heath22@yahoo.co.uk" <iona.heath22@yahoo.co.uk>
Sent: Thursday, 22 May 2014, 16:53
Subject: BMJ Statin papers

To Whom it May Concern

I am writing to express my support for the request that the BMJ retract both papers from the journal. I believe that the facts have been overrepresented and could have untoward repercussions

My concern is that patients at high risk of vascular events may well be deterred from continuing or starting statin therapy unless these misleading papers are withdrawn entirely from the medical literature.
The two papers contain several … misrepresentations of the evidence about the safety of statin therapy (e.g. claims that side-effects are caused in 18-20% of patients, and myopathy in 5% of patients: see attached papers with annotations), and more generally about cholesterol and coronary disease… (see attached BMJ correspondence).
Both authors also assert that the evidence from the randomized trials of statins cannot be trusted because, in their view, none of them was conducted independently and adverse event data were not systematically recorded or reported.
The BMJ recently published a partial correction of one… misrepresentation of the evidence in both papers, but it did so in a way that was not clear (see attached editorial and corrections) and it has not dealt at all with the many other misleading claims about the rate of side-effects that have been drawn to its attention.

Yours sincerely

B J Gersh
Mayo Clinic College of Medicine

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G.I.S.S.I. – H.F. Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca Associazione Nazionale Medici Cardiologi Ospedalieri – ANMCO Istituto di Ricerche Farmacologiche "Mario Negri"

ANMCO: Via Alfonso La Marmora, 36 – 50121 Firenze Tel. +39 055 5101361 – Fax +39 055 5101310 – E-mail: gissihf@anmco.it- Web: www.anmco.it IRCCS Istituto "Mario Negri": Via Giuseppe La Masa, 19 – 20156 Milano Tel. +39 02 39014.482/407 – Fax +39 02 33200049 – E-mail: depcardio@marionegri.it - Web: www.marionegri.it web: www.gissi.org

Florence, May 22, 2014
Dear Prof Heath,
I would like to enter in the debate regarding the articles by Abramson (1) and Malhotra (2) reporting some observations derived from a trial on the effect of statins in heart failure (HF) conducted in my country, the GISSI-HF Trial (3).

The GISSI-HF trial tested the effects of rosuvastatin versus placebo on the primary end-point of all-cause death or hospitalizations due to cardiac reasons in 4574 patients with HF.
I think that the data on the safety aspects of rosuvastatin collected in this trial can add something relevant to the current discussion. Patients recruited in GISSI-HF were particularly fragile: all of them had a documented diagnosis of HF; as all the patients with this clinical condition, they were treated with several drugs; renal dysfunction was very frequent; age was advanced (44% of them was aged more than 70 years).

In this context of a real high risk of adverse reactions, muscle-related symptoms occurred in 23/2285 patients randomly allocated to rosuvastatin and in 21/2289 of those allocated to placebo.
These figures are obviously very far from the figures shown by Abramson in his article, but this is not surprising to me, since it is well known that the rate of adverse reactions reported in non-controlled studies generally overestimates the risk of drug related events. You can surely remember the cases of the high rate of cough reported for ACE-inhibitors or that of erectile dysfunction reported for beta-blockers. The randomized clinically studies testing these drugs confirmed the excess of these specific adverse reactions but the real excess with respect to placebo was much lower than that reported without a control group in the observational research.
Concerning the issue of a potential conflict of interest, the GISSI-HF trial has been conducted in a totally independent way since the design of the study, the conduction, the monitoring, the property of the database, the analysis and the reporting of data were conducted by the GISSI Group, a partnership of two non-for-profit Institutions, the Mario Negri Institute for Pharmacological Research and the Research Center of the Italian Association of Hospital Cardiologists.

The scientific and lay articles of Abramson can really determinate a negative impact on starting/continuation of statin treatment in patients at any level of cardiovascular risk with the consequence to reduce the favorable effect that this treatment produces in the prevention of vascular events.

For this reason, I am strongly in favor of the proposal to retract the quoted articles from the BMJ.

Best regards
Aldo P. Maggioni, MD
Member of the Steering Committee of the GISSI-HF Trial
Director of the Research Center of the Italian Association of Hospital Cardiologists (ANMCO)

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22.5.14
Dr Iona Heath
Chair of the Panel to evaluate the reports in BMJ about Adverse effects of statins

We, the undersigned, strongly recommend the panel to advise retraction of the reports by Dr, Abramson et al and by Dr Malhotra in BMJ 22. October 2013.They both publish data that are false and misleading and may prevent people at risk of atherosclerotic disease from receiving statins. As lead investigators and chairs of steering committees of statin trials and with experience from safety monitoring boards of trials, we feel confident that the published information from original statin trials reflect the true safety and adverse reaction rates in the trials. When monitoring safety data the safety committee in such trials receive complete records of all adverse experiences reported by the investigators. The Scandinavian Simvastatin Survival Study (4S) was the first clinical trial reporting the effect of a statin on survival and clinical endpoints[1] and on safety of the drug[2]. This trial was carried out in an era when cholesterol lowering was under attack for being responsible for various life-threatening conditions[3]. Therefore the investigators of 4S were particularly sensitive to any adverse events occurring among the patients. The investigators reported all adverse experiences, serious or not, which provided the basis for publications. We found no excesses of any adverse experience, but one case of myopathy in a patient started on diltiazem along with simvastatin. 4S was a trial of particularly high standard with no patient lost to follow-up and meticulous source control of all recorded information. It set the standard for future trials. Practicing physicians should be guided by original data from randomized controlled trials, not from misunderstood observational studies.

1. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383-89.
2. Pedersen TR, et al. Safety and tolerability of cholesterol lowering with simvastatin during 5 years in the Scandinavian Simvastatin Survival Study.. Arch Intern Med 1996:156:2085-92
3. Muldoon MF, et al. Lowering cholesterol concentrations and mortality: a quantitative review of primary prevention trials. BMJ 1990;301:309-11

Terje R. Pedersen, MD
Professor of medicine
Oslo University Hospital
Lead investigator of 4S
Chairman of the IDEAL study
Chairman of the SEAS study

John Kjekshus, MD
Professor emeritus
Oslo University Hospital
Chairman of the Steering Committee of 4S
Member of the DSMB of the SEAS study
Chairman of the CORONA study

Conflict of interest: We have both received research support, speakers honoraria and consulting fees from several pharmaceutical companies producing statins.

From: Terje Pedersen <t.r.pedersen@medisin.uio.no>
To: Iona Heath <iona.heath22@yahoo.co.uk>
Sent: Monday, 26 May 2014, 10:06
Subject: Re: BMJ Panel on Statin papers

Dear Dr Heath
We did not send [a rapid response to the BMJ]. Both of us were first made aware of the papers through a news report on Norwegian state TV last week where the

case was presented and Dr Rory Collins was interviewed. Dr Collins is a close collaborater of mine, and I am a member of the Steering Committee of the trials of lipid lowering carried out by the CTSU of the Oxford University. I would like to add that I have for the last few years been lecturing about the myth of statin muscular problems, a myth that arose in the 1980s when MSD provided lovastatin and later simvastatin for compassionate use to US lipid clinics for treatment of patients with familiar hypercholesterolemia. At that time the pharmacokinetics of these statins were not well known, in particular the adverse effect on metabolism of statins when combined with gemfibrozil. Several FH patients on gemfibrozil developed myopathy or rhabdomyalisis and the statins were blamed. When we launched the 4S we were informed that all patients participating in the trial should be warned and queried about muscular problems. Since gemfibrozil was not used in the trial we did not see any case of myopathy except the one case where the patient was started on diltiazem which also is metabolized by CYP 3A4.

Kind regards,

Terje Pedersen

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Jonathan A Tobert MB, BChir, PhD, Tobert Medical Consulting LLC
3 Red Fox Trail, Warren, NJ 07059-6834, USA
+1 (732) 271-0205 jtjat@optonline.net
22 May, 2014
Dr Iona Heath

Dear Dr Heath,

I am writing to express grave concerns about the reluctance of the BMJ to retract the paper by Abramson et al. Unless retracted, it will cause substantial further harm by discouraging doctors and patients from using statins appropriately because of unfounded concerns about safety. But no drug class has been better studied, including large randomised clinical trials (RCTs) over 25 years, from which it is clear that statin therapy substantially reduces cardiovascular morbidity and mortality with minimal adverse effects in a broad array of patient types. Furthermore, most statins are now generic, and therefore cheap and very cost-effective to prevent myocardial infarctions and ischaemic strokes.

1. *Summary of my argument.*
The statement that statins cause adverse effects in about 20% of patients is not a minor error, not just a detail buried in the text. Rather, it is a major falsehood appearing in a box summarising the article. Furthermore, correcting *this falsehood destroys the main conclusion of the paper,* that in low risk patients the hazards of statins outweigh the benefits: at the top of the paper "A review of statins for primary prevention of cardiovascular disease could alter guidance for those with a 10 year risk of less than 10%. John Abramson and colleagues argue that statins have no overall health benefit in this population and that prescribing guidelines should not be broadened". Having acknowledged the error in a published correction, their case collapses and the new conclusion should be exactly the reverse, that the benefits outweigh the risk. Thus this paper is misconceived and reaches a false conclusion. If the goal is to prevent further dissemination of this false conclusion and discrediting of the BMJ, clearly the way to achieve this is to retract the paper. Merely publishing a narrow correction of the falsehood is not nearly enough, because it leaves uncorrected the original conclusion.

2. *The authors' knowledge of the field and conflicts of interest*
…

3. *Who am I to comment?*
I have been involved with clinical trials of statins for most of my professional life as a research physician, publishing my first statin papers in the early 80s (1, 2), and have reviewed the field in general (3) and simvastatin in particular (4). I worked for Merck Research Laboratories from 1976 until retiring in 2004 and starting my own consulting company. I led the team that developed lovastatin (mevinolin) and designed the clinical development programme for this drug, the first statin available for prescription (in the US and other countries, 1987). Later I worked extensively on simvastatin, the first statin available in Europe (1988). In 1987, I recognised one of the first cases of myopathy and introduced the term myopathy (in the context of statin therapy) to the literature and defined it (5). I am therefore very familiar with the evidence for both benefit and safety, but I should add that I have no conflict of interest of any kind: I am an independent consultant, with no financial interest or share ownership in Merck or any other health-care company, and I have never served as an expert witness.

4. *The 20% adverse effect rate is an… error*
…The overall rates of serious adverse effects or adverse events causing discontinuation of allocated treatment in statin RCTs are usually comparable in the statin and placebo groups, and the risk of the

hallmark statin adverse effect, myopathy (including rhabdomyolysis) is very low. There may also be a small excess risk of developing diabetes. To take two examples among many, in JUPITER (6), which compared rosuvastatin 20 mg versus placebo in 17, 802 patients for 1.9 years, the total numbers of reported serious adverse events were similar in the rosuvastatin and placebo groups (1352 and 1377, respectively), and myopathy occurred in 10 subjects receiving rosuvastatin and 9 receiving placebo. In the 20,536 patient Heart Protection Study (7) comparing simvastatin 40 mg against placebo over 5 years, 4.8% of participants in the simvastatin group stopped the allocated treatment due to adverse events, compared to 5.1% in the placebo group. The incidence of myopathy was <0.1% greater in the simvastatin group compared to the placebo group (8).

The data in the prescribing information are derived largely from randomised clinical trials (RCTs), because regulatory agencies know that RCTs are by far the most reliable source of information available, regardless of the funding source… Do they really believe that "real-world experience" is somehow superior to carefully conducted and hugely expensive placebo-controlled trials with tens of thousands of patients followed for several years and questioned about adverse effects at regular clinic visits? If uncontrolled observation is somehow better, why bother with RCTs?

5. *Dismissal of RCTs funded by pharmaceutical companies.*
The authors also imply that the pharmaceutical companies that typically sponsor these trials suppress data on adverse effects: they write "All of the randomised controlled trials included in the CTT meta-analysis were funded by the manufacturer of the statin being studied." There have certainly been rare cases of fraud and misconduct by employees of drug companies, and more commonly a tendency for them to be slow publishing studies that fail to demonstrate efficacy, but these issues are also true of employees of academic medical centres, and do not justify dismissing *en masse* clinical trials funded by the industry. As noted above, I worked for Merck, the manufacturer of lovastatin and simvastatin, for 27 years, and I can report that I never felt any pressure to suppress data of any kind including safety data; quite the contrary, the culture insisted on accurate accounting of data, mainly because of ethical reasons, but also because failure to report safety data appropriately to regulatory agencies carries a high risk of regulatory sanctions and adverse publicity, and in the US has occasionally resulted (not at Merck) in a prison sentence.
As an example of the advantages of RCTs (however funded) for uncovering adverse effects, simvastatin 80 mg is rarely prescribed today. This is a direct consequence of a large randomised controlled trial conducted by the University of Oxford and funded by Merck, in which the incidence of myopathy was approximately 1% at this dose, compared to 0.02% at 20 mg (9). The study also revealed previously unknown drug interactions relevant to simvastatin 80 mg. These findings led to changes to the *Warnings and Precautions* section of the prescribing information, providing these data and strongly discouraging the use of 80 mg. Over 20 years of "real-world experience" did not uncover these data, but a clinical trial did.

Sincerely,
Jonathan A Tobert MB, BChir, PhD

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Naveed Sattar
Professor of Metabolic Medicine
BHF Glasgow Cardiovascular Research Centre
University of Glasgow, Glasgow, G12 8TA
Mob: 07971 189415

PA: Ms Lyndsey Macdonald
Lyndsey.macdonald@glasgow.ac.uk
Phone 0141 330 7615

Dear Professor Heath,

My colleague, Prof Naveed Sattar, and I are writing to you regarding the recent statin related papers published in the BMJ. We are based at the University of Glasgow and have published what we consider to be important data regarding effects of statins in the last 3 years (Lancet 2010, JAMA 2011 and 2012) - importantly, the findings have been based on randomised trial data in all cases... While it was correct to retract specific erroneous statements which misquoted another paper, other incorrect statements are made in both cases and these should be seriously challenged or retracted.

In addition, we suggest that your panel seriously considers asking the BMJ editorial board to treat pharmaco-epidemiological studies, which seek/claim causal relationships with various outcomes, with great caution during the peer review process; and that the substantial weaknesses of this form of observational data are always highlighted. Indeed, the journal would benefit from a serious and open debate about this issue, perhaps as a published article with proponents and opponents thereof, or in some other way.

Thanks for your attention and best wishes,

David Preiss and Naveed Sattar

Dr David Preiss
MBChB MRCP FRCPath PhD
Clinical Senior Lecturer and Honorary Consultant in Metabolic Medicine
BHF Glasgow Cardiovascular Research Centre
University of Glasgow

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Connie B. Newman, M.D. **New York University School of Medicine 550 First Avenue, New York,** N.Y. **10016 USA** cncbn@optonline.net connie.newman@nyumc.org

May 22,2014

Dr. Iona Heath
Chair, BMJ Panel

Dear Dr. Heath,

I am writing to address some of the misinformation conveyed in the report by John D Abramson and colleagues (Should people at low risk of cardiovascular disease take a statin? BMJ 2013; vol 347:f6123). The authors misrepresent the safety of the statin class of drugs and should this paper remain in the literature, it would certainly raise concerns among physicians (and patients) about the use of statins. This could easily result in a negative impact on public health, by increasing cardiovascular disease, which has been declining in the past several decades. For these reasons I believe that this paper should be retracted.

Abramson et al also make unsubstantiated allegations about the pharmaceutical industry, and the clinical trials funded by the industry. Specifically the authors state that industry-sponsored clinical trials are more likely to report favorable efficacy and safety results and conclusions. They claim that this is due to under-ascertainment and selective reporting of adverse events (including serious adverse events). In my experience, this is not so.

I am currently Adjunct Associate Professor of Medicine at New York University School of Medicine, and have held this position for the past 7 years, since 2007. From April 2001 to February 2007 I was employed by Pfizer, Inc. where I held positions in both Worldwide Regulatory Affairs and Worldwide Medical. Among my responsibilities included the accurate reporting of clinical trial and other data both efficacy and safety -for the product atorvastatin to regulatory authorities worldwide. One of our goals was to protect patient safety by identifying unexpected and expected adverse events possibly related to atorvastatin, and ensuring that these adverse events were fairly represented in the prescribing information for atorvastatin worldwide. We evaluated data from randomized controlled clinical trials (including trials funded by Pfizer), spontaneous adverse event reports, and the medical and scientific literature. Many of the Pfizer sponsored clinical trials were conducted by independent investigators. We were committed to scientific truth and accuracy. We certainly did not report only favorable efficacy and safety results, as shown by the following example, from the SPARCL (Stroke Prevention by Aggressive Cholesterol Lowering) trial.

SPARCL, a placebo-controlled trial, funded by Pfizer, of atorvastatin 80 mg in about 4700 patients with prior stroke or TIA and no history of coronary heart disease evaluated the effects of atorvastatin 80 mg on the primary endpoint of fatal or non-fatal stroke. Median follow-up was 4.9 years. Atorvastatin 80 mg significantly reduced the risk of fatal or non-fatal stroke by 15% (HR 0.85; 95% CI, 0.72-1.00; p=0.05 or 0.84; 95% CI, 0.71-0.99; p=0.03 after adjustment for baseline factors) compared to placebo. This benefit was largely due to a reduction in ischemic stroke, as shown by a post hoc analysis of the data. However, the post hoc analysis of the data, also found, unexpectedly, that atorvastatin 80 mg increased the incidence of hemorrhagic stroke (55/2365, 2.3% vs. 33/2366, 1.4%, p=0.02) compared to placebo. Further analysis showed that patients

with previous hemorrhagic stroke or lacunar infarct were at increased risk of hemorrhagic stroke. The decision to add this information to the warnings sections of atorvastatin labels worldwide was made promptly. There was never any resistance within the company. Section 4.4 of the EU SPC for atorvastatin states:

"Section 4.4 *Special warnings and precautions for use*

Stroke Prevention bv Aggressive Reduction in Cholesterol Levels (SPARCL)

In a post-hoc analysis ofstroke subtypes in patients without coronary heart disease (CHD) who had a recent stroke or transient ischemic attack (T/A) there was a higher incidence of hemorrhagic stroke in patients initiated on atorvastatin 80 mg compared to *placebo. The increased risk was particularly noted in patients with prior hemorrhagic stroke or lacunar infarct at study entry. For patients with prior hemorrhagic stroke or lacunar infarct, the balance of risks and benefits of atorvastatin 80 mg is uncertain, and the potential risk of hemorrhagic stroke should be carefully considered before initiating treatment (see section* 5.1}."

"Real world experience" failed to detect this effect on hemorrhagic stroke.

Sincerely,
Connie Newman, M.D.
Adjunct Associate Professor of Medicine
NYU School of Medicine
Department of Medicine
Division of Endocrinology, Diabetes and Metabolism
550 First Avenue New York, NY 10016

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From: "Sever, Peter S" <p.sever@imperial.ac.uk>
To: "iona.heath22@yahoo.co.uk" <iona.heath22@yahoo.co.uk>
Cc: Rory Collins <rory.collins@ctsu.ox.ac.uk>
Sent: Friday, 23 May 2014, 11:47
Subject: Abrahams and Malhotra

Dear Dr Heath
As chairman of the panel set up by the BMJ to consider the question of whether a full withdrawal of the Abrahamson and Mahotra papers relating to side effects of statins should be expedited, I write to provide my full support of the detailed case made by Rory Collins…, the consequence of which, is that for the wrong reasons patients, whose future morbidity and mortality from cardiovascular disease would have benefited substantially from statin therapy ,will be dissuaded from taking the drugs or discontinuing them if they are already receiving treatment.
The BMJ has taken a strong position on scientific integrity and its detailed review and condemnation of the Lancets publication of the Wakefield MMR scandal was well received. The same principles should apply over the critical reviews of these two statin papers and the misrepresented claims of Zhang et al ,that statins were causally related to side effects in 20% of statin users.
AS the Co-chief Investigator of ASCOT , a trial that was independently designed and lead, and where the executive committee held the data base, analysed the results and published the papers independent of the funder, Pfizer, I strongly refute the implications of authors of the 2 recent studies implying that trial sponsors could have influenced the results and downplayed the side effect profiles of the drugs.
In ASCOT, side effect profiles were identical on those taking placebo and statin Interestingly in the blood pressure arm of ASCOT we detected drug related side effects of the ACE inhibitor (cough) and the calcium channel blocker (ankle oedema) with incident rates not dissimilar from those experienced in clinical practice. So if statins were to be causally related to myalgia/ myopathy , why did we not detect this in a trial of 10,000 subjects ?
I would like to remind you that in a recent study published in Archives, a rechallenge of patients previously withdrawn from statin because of muscular side effects, yielded the return of identical symptoms in 80% of patients. Problem was the rechallenge was a placebo !

We are dealing with a very serious issue here, and editors of major international journals have a duty to publish good science and not popularize bad science which is regretably the prerogative of the lay press. The retraction of these two papers will go some way towards damage limitation, but do not underestimate the huge impact these publications will have had and the disastrous consequences for the vulnerable patient population who stand to benefit enormously from their statin treatment.

Peter Sever
Professor of Clinical Pharmacology
National Heart and Lung Institute
Imperial College London

8
From: Scott Grundy <Scott.Grundy@UTSouthwestern.edu>
To: "iona.heath22@yahoo.co.uk" <iona.heath22@yahoo.co.uk>
Sent: Friday, 23 May 2014, 22:39
Subject: Statin papers

Dear Sir/Madam:

Dr. Rory Collins contacted me about papers published in the BMJ by Dr. Aseem Malhotra and Drs. Abramson et al. I have examined these papers…The paper by Abramson et al. fails to make a cogent assessment of why people at so-called "low risk" should avoid statins. This is an area that needs critical assessment, but the paper by Abramson et al. does not do justice to the question and gets off onto the area of statin side effects. In truth, some people cannot tolerate statins, but little is known about the extent of the problem and is undoubtedly overstated by the authors. I agree with Dr. Collins that these papers do not do justice to the usual scientific standards of the BMJ. I see nothing wrong with retracting the papers.

Sincerely,
Scott M. Grundy

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From: KZ Davey-Smith <KZ.Davey-Smith@bristol.ac.uk>
To: iona.heath22@yahoo.co.uk
Sent: Monday, 26 May 2014, 15:43
Subject: Fwd: Review of BMJ papers on statins

Dear Professor Heath

I am emailing you in your capacity as chair of the BMJ committee set up to investigate the statin papers. I feel that the publicity these papers received constitutes a serious threat to UK population health improvements strategies. I feel I can hardly be seen to be a cheerleader for the pharmaceutical industry, mass unjustified polypharmacy or indeed cholesterol lowering without evidence; in 1992 I published a paper in the BMJ (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1881265/pdf/bmj00060-0042.pdf), based on primary prevention trials that had been carried out before there was any large scale RCT evidence on statin effectiveness and safety, stating that evidence on such trials was required before there should be efforts to increase cholesterol lowering pharmacotherapy in the primary prevention setting. In 1993, also in the BMJ, I published a meta-analysis suggesting a cut off level for risk of coronary heart disease which should be utilized for decision making in respect to which groups it was appropriate to instigate such treatment, again before the statins trials appeared. Such risk-based approaches have become common place. Since then statins have undergone evaluation to a degree unprecedented for any such medication, and it is clear that appropriate randomized data demonstrate that they are effective, with remarkably low side effects, and it is clear that the risk thresholds for treatment instigation should be decreased from those used previously. The BMJ papers dramatically over-estimated side effects and misrepresented the latest Cochrane review on which I was an author. I think a much stronger position should be taken by the BMJ in publicizing the fact that the journal published misleading information, with potentially serious public health consequences.

Best wishes
George Davey Smith

The panel asked of George Davey Smith, in relation to the sentence: "*The BMJ papers dramatically over-estimated side effects and misrepresented the latest Cochrane review on which I was an author".*

1. to list specifically the facts which he says were misrepresented in the latest Cochrane review on which he was an author
2. what his view is on completeness of reporting of adverse events in clinical trials?"

GDS response:
3.6.14: Regarding the Cochrane review see the response from Huffman et al on BMJ website (http://www.bmj.com/content/347/bmj.f6123/rr/678736).

Regarding the question on side effects, and the ascertainment of these, the only way to obtain meaningful data of those caused by the treatment is within the randomized controlled trial setting, when assessment of side effects is blinded to treatment. The remarkable finding is that statin use shows very limited evidence of real (i.e. drug induced) side effects, beyond some very rare events. The notion that there may be differences in side effects that are not ascertained through the methods used in randomized controlled trials is not tenable. The issue is straightforward - most of these "side effects" reflect symptoms which have a distribution, in that situation it's very difficult to think of how ascertainment

methods applied blindly and in the same way for active treatment / placebo could lead to no difference at one threshold and a meaningful difference at another threshold. The same is true for 1/0 outcomes if considered on a liability model (see, e.g.: Falconer et al. The inheritance of liability to certain diseases, estimated from the incidence among relatives. Ann. Hum. Genet., Lond. (1966),29, 61). One clear indication with a 1/0 outcome that the trials are getting the right answer relates to diabetes, with a robust indication of a small, increased risk of statins. The way of ascertaining the side effects generated a replicable answer across trials, and also one that agrees with Mendelian randomization studies of HMGCoA genetic variation that mimics statin activity and diabetes (to appear in the Lancet soon I think). The possibility that pre-randomisiation run in periods excluded large numbers of individuals who would have developed side effects is not a tenable explanation across the large RCTs which had different practices in this regard. Overall I think it is difficult to put together a coherent argument that allows for major differences in side effects not ascertained in the trials,

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From: Emily Banks <Emily.Banks@anu.edu.au>
To: "iona.heath22@yahoo.co.uk" <iona.heath22@yahoo.co.uk>
Sent: Sunday, 25 May 2014, 13:10
Subject: need to withdraw articles

Dear Professor Heath,

I write to urge the British Medical Journal to formally withdraw the papers (and related correspondence) about statins by Abramson et al and by Malhotra that were published in October 2013, as the only truly effective means of mitigating the ongoing public health risks related to the misinformation contained in them.

Throughout history, misinformation has been a major, if not *the* major, public health hazard. The British Medical Journal has played an important role in dispelling numerous health-related misconceptions over the years. Statins are highly effective for the primary and secondary prevention of cardiovascular disease (CVD). The unwarranted cessation and non-use of statins, when indicated, due to misinformation will result in excess cardiovascular events and deaths. Conservative estimates, based on a number-needed-to-treat of 50, mean that for every 100,000 people in whom statins are indicated who cease them, around 2,000 additional excess CVD events will occur. Hence, the likely effects of these articles, and their continuing availability, have the potential to be large, particularly compared to other public health hazards (e.g. epidemics, natural disasters) where prompt and effective action is considered mandatory.

The articles by Abramson et al and by Malhotra contain a number of serious errors, which have already been pointed out, predominantly relating to exaggeration of harms/adverse events attributed to statins, and an underestimation of benefits. These errors have not been addressed adequately in subsequent statements and, unless withdrawn, will continue to undermine the accurate understanding of the risk/benefit profile of statins, and will continue to be cited.

Best wishes,

Yours sincerely,

Emily Banks

Potential conflicts of interest: I have no competing interests to declare. I currently serve as the Chair of the Advisory Committee on the Safety of Medicines; the views expressed in this letter are my own.

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BRIGHAM AND WOMEN'S HOSPITAL

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May 28, 2014

Dear Members of the Independent Statins Review Panel:

I write to you regarding your important charge to advise the *British Medical Journal (BMJ)* regarding the possible retraction of the articles by J. Abramson, et al. and A. Malhotra. I have, of course, read these two papers, the paper by Zhang et al., the two corrections published in the *BMJ* and the on-line letters and responses regarding these papers also published by the journal.

…

Sadly, the articles by Abramson et al and Malhotra made two serious errors. The first was to present the paper by Zhang et al … out of context and report an 18-20% "side effects of statins". Simultaneously, they clearly miscalculated the
number of patients needed to have their LDL-C reduced to prevent one major coronary event or stroke. I do not understand the reasons for these errors. These problems are compounded by the awkwardness of the corrections which simply repeat some of the misleading statements.

Of course, reporting on disagreements between what are perceived to be "medical authorities" who publish their controversial views in a prestigious journal makes excellent material for the public press. The unfortunate victims are patients who don't wish to take medications and who use these "perceived arguments" as reasons to discontinue or not begin statin therapy when such use is indicated by practice guidelines. This is a threat to their health.

This is an unfortunate situation, and it could have been prevented at the time of the initial reviews or after the problems were pointed out. At this time, it seems to me that the only viable remedy is total retraction of the two papers and I hope, with respect, that you will agree.

Sincerely yours,

Eugene Braunwald, M.D.

Disclosures:

1) I chair the IMPROVE-IT trial, sponsored by Merck which is studying the potential benefit and risks of the addition of ezetimibe (Zetia) to a statin in patients who have recovered from an acute coronary event.
2) I serve as deputy chair of the Steering Committee of the REVEAL trial, also funded by Merck, which is studying the clinical effects of a novel drug, anacetrapib, on clinical outcomes in patients with a history of myocardial infarction.

In both instances Merck provides financial support to the Brigham and Women's Hospital in Boston but not to me. I receive reimbursement for clearly identified expenses associated with these trials.

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Tony Keech <Tony@ctc.usyd.edu.au>
29 May 2014, 7:11

to iona.heath, harlan.krumholz

Dear Panel
Please find attached a submission for consideration. It is beyond your very tight advertised timeline offered for submissions after the BMJ Editors' Corrections, even though they have taken about 6 months to appear. We are hoping you will therefore consider them in full.
Yours sincerely
Anthony Keech and Jordan Fulcher

Independent statins review panel

We write to support the proposal that the two papers being reviewed by this panel should be formally withdrawn by the journal.

The scale of the potentially harmful impact on public health of their original publication including the serious misquotations of Zhang's work and the prolonged period from publication until the editors' corrections is hard to quantify.

We agree with the arguments set out by Professor Collins in his submission to the panel. Of further concern, the correction published for Malhotra's paper is in our view sufficiently vague that many readers will not clearly understand what the issues were about the misquoted data. In both manuscripts and their subsequent corrections the scale of reports of perceived side effects of statin treatment amongst patients in fact allocated to placebo identified in randomised controlled trials is not acknowledged, producing a distorted impression of the magnitude of side effects attributable to statin therapy (and hence to be balanced against reported benefits).

In particular the incomplete presentation and scientific consideration of Zhang's side effect data in the Abramson paper appears to have been central to the arguments made (ie. that the benefits of statin therapy do not outweigh the risks in lower vascular risk patients) and content of the included table of bullet points.

We recognise this submission is beyond the advertised deadline but hope the panel is willing to consider it.

Professor Anthony Keech
Deputy Director, NHMRC Clinical Trials Centre, University of Sydney NSW Australia

Dr Jordan Fulcher
Cardiologist / Research Fellow
NHMRC Clinical Trials Centre, University of Sydney NSW Australia

Conflicts of Interest:
AK was an original Co-PI of the Heart Protection Study, is a member of the LIPID trial executive committee, was part of the Pravastatin Pooling Project collaboration, chair of the FIELD trial and is an executive committee member of the FOURIER trial, each evaluating effects of statins or other lipid modifying treatments. AK and JF are members of the Cholesterol Treatment Trialists' Collaboration Sydney co-ordinating centre. AK and JF have both received lecture fees from pharmaceutical companies manufacturing statins.

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From: N Wald <n.j.wald@qmul.ac.uk>
To: "iona.heath22@yahoo.co.uk" <iona.heath22@yahoo.co.uk>
Sent: Thursday, 29 May 2014, 11:20
Subject: Independent panel on adverse effects of statins

Dear Dr Heath

We write in connection with the scientific concerns expressed to the BMJ by Sir Rory Collins over the scientific integrity and validity of the paper by Abramson, Rosenberg, Jewell and Wright published in the BMJ on 22 October 2013 and the paper by Malhotra published in the same issue.

We attach our assessment of the two papers.

We would like to disclose that we are inventors of the "Polypill" and have presented evidence for over 10 years to show that such a preventive medication would have substantial public health benefits, and to help promote its development we have interests in patents in Europe, USA and Canada.

We hope our comments are helpful to you and your colleagues.

Yours sincerely
Nicholas Wald
Malcolm Law

Attachment
Assessment on Abramson et al and Malhotra, BMJ, October 22 2013

We write to you in your capacity as Chair of the Review Committee set up by the BMJ to consider whether two BMJ papers, one by Abramson et al[1], and the other by Malhotra[2], should be entirely retracted.

1. Paper by Abramson et al

Efficacy

Abramson et al… underestimate the efficacy of statins.

These authors do not dispute the results of the meta-analysis of the Cholesterol Treatment Trialists (CTT) Collaboration, which showed an estimated 26% reduction in major coronary events for a 1.0 mmol/L serum LDL cholesterol reduction.[3] This is an estimate of the short term effect, since little reduction in coronary heart disease (CHD) events takes place in the first two years after lowering cholesterol, and the long term reduction in major coronary events is an estimated 36% per 1.0 mmol/L LDL cholesterol reduction (as published in the BMJ[4]). Atorvastatin 20mg reduces LDL cholesterol by about 2 mmol/L[4], which would be expected to reduce the risk of major coronary events by about 60%. These estimates come from meta-analyses in which only "hard" endpoints (CHD death or non-fatal myocardial infarction) were included.[3,4] Abramson et al have not recognized this longer preventive effect.

Abramson et al make a serious epidemiological error in basing their assessment of efficacy on all-cause mortality. All cause mortality is not the correct outcome to use because it is insensitive to the assessment of both benefits and hazards. Moreover there is no need for an "arbiter" because the CTT meta-analyisis showed no increase in non-vascular causes of death (relative risk 0.97).[3] Using all-cause mortality greatly reduces statistical power even for a common cause of death; about 1 in 5 people in the general

population die of a heart attack, so the reduction will be diluted by the 80% of other deaths. Measles vaccine was introduced because trials showed that it prevents measles, nobody demanded a reduction in all-cause mortality. The correct approach is to examine CHD specific changes and separately determine whether there is any evidence of an increase in risk of other disorders. Nonetheless, the CTT meta-analysis was sufficiently large to demonstrate a reduction in all-cause mortality[3] and these results were inappropriately used by Abramson et al in an invalid analysis. They performed a calculation (the details of which are not described) to determine a level of risk at which the reduction in all-cause mortality becomes no longer statistically significant. They then make the… error of interpreting a change that is not statistically significant as evidence of no effect, even though the confidence interval on their risk estimate (14% reduction to 4% increase) contains the expected reduction in all-cause mortality (about 10%).[1] Such an analysis is spurious, because there must necessarily be a point where an effect is no longer discernable, even though the effect is present and this error is made worse by use of the insensitive outcome of all-cause mortality.

Adverse effects
Abramson et al… overstate the risk of adverse effects of statins.

Myopathy The estimate from randomised trials cited by the CCT of the excess risk of myopathy in people regularly taking a statin compared with people who are not is about 0.5 per 1000 persons over five years.[3] This is a reasonable estimate, and somewhat higher than that of 0.05 per 1,000 from a meta-analysis of randomised trials.[5] Abramson et al are wrong to dismiss the estimates, and give no reason for doing so. Instead, they used an estimate of 18% from an observational study.[6] Muscle symptoms are common, regardless of taking statins. The correct estimate of the risk of muscle symptoms caused by statins should be derived from subtracting the prevalence in people taking a placebo from that in people taking a statin. Abramson et al ignore the fact that symptoms in a person taking a drug are not necessarily caused by that drug, in spite of the fact that the authors of the observational study concluded in their paper that in their study "many statin-related events may have other causes[6]". It was wrong of Abramson et al to disregard this.

Diabetes The best estimate of the risk of diabetes in people taking statins comes from a group of 33 trialists from 11 research centres publishing in the Lancet.[7] They estimated that treatment of 255 people with statins for four years would cause one extra case of diabetes and concluded that "the risk is low both in absolute terms and when compared with a reduction in coronary events". Abramson et al do not cite this estimate, but instead cite estimates from trials with values above the average from all trials and ignore estimates from trials in which risk fell below the average…

Others disorders Abramson et al produce a list of symptoms that have been reported in observational data on people taking statins. They do this uncritically without attention to the fact that not all symptoms occurring in people taking a drug are caused by that drug (as above). They also ignore confounding. There have been many published reports of observational data suggesting both lower and higher prevalence of various symptoms and illnesses in people taking statins (lower risk of hip fracture is one such example[8], and oesophageal cancer (in a report cited by Abramson et al[1]) is another). People who choose to take statins tend to have higher income and higher levels of education than people who do not.[9,10] As a result, statins will be associated with a lower risk of disorders associated with lower socio-economic status (such as hip fracture) and a higher risk of disorders associated with higher socio-economic status. Implying causality from such associations is misleading.

2. Paper by Malhotra

Malhotra's paper amounts to little more than opinion...The most recent comprehensive meta-analysis of randomised trials of dietary change and serum cholesterol (published in the BMJ!) yielded the estimate that "isocaloric replacement of saturated fats by complex carbohydrates for 10% of dietary calories

resulted in blood total cholesterol falling by 0.52 mmol/L[11]". This translates into a substantial and worthwhile effect in preventing coronary heart disease. Malhotra also resurrects the "cholesterol controversy" of 20 years ago in which observational evidence was inappropriately used to justify a view that lowering cholesterol increases non-cardiac mortality. It was shown in 1994 (again in the BMJ!), that the association of relatively low serum cholesterol with suicide and cancer arose because depression and cancer both lower serum cholesterol through causing anorexia (so-called reverse causality).[12]

In summary
Both papers are… flawed and misrepresent prior published study results. The Lancet retracted the paper by Wakefield and his colleagues who incorrectly claimed that the MMR vaccine caused autism and should not be used, thereby falsely casting doubts about an important preventive intervention. The BMJ now finds itself in a similar position.

Retraction of the two papers will help to set the record straight and correct the serious misrepresentation of sound evidence on the efficacy and safety of statins and on the efficacy of dietary saturated fat reduction in the prevention of the common cause of death in the UK.

In addition, the conduct of the BMJ is of concern. It was slow to respond to the concerns over the scientific integrity and validity of the two papers, it permitted further incorrect assertions in support of the papers, it accepted only part of the errors made, and it passed responsibility for the error onto its reviewers instead of the Editor accepting the error and acting decisively instead of passing the responsibility onto your committee.

Malcolm Law FRCP
Sir Nicholas Wald FRS

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London EC1M 6BQ
28 May 2014

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