SP7 & SP8 – Post-publication emails between John Abramson and The BMJ (Helen MacDonald and Fiona Godlee)

From: jburrell@bmj.com [jburrell@bmj.com] On Behalf Of Fiona Godlee [fgodlee@bmj.com]
Sent: Monday, March 24, 2014 8:34 AM
To: Abramson, John David
Subject: Statins - Rory Collins versus the BMJ

Dear John

You will be aware of the spat between Rory Collins and the BMJ on the side effects of statins. See links to the Guardian story and the BBC Radio 4 discussion on Saturday.

http://www.theguardian.com/society/2014/mar/21/-sp-doctors-fears-over-statins-may-cost-lives-says-top-medical-researcher

http://bbc.in/1gIkCRX

All good stuff. And I'm glad to hear Rory confirm that he plans to send us an article presenting his position on side effects of statins. It will be interesting to see what he has to say.

I hope all continues well with you.

Best wishes.Fiona

On 22 April 2014 12:57, Fiona Godlee <fgodlee@bmj.com> wrote:
Dear John, I would welcome your thoughts on the attached letter from Rory Collins. I will ask him (again) to send a letter for publication, to which I will then ask you to respond. My question to you is whether you think that a correction is needed to your article in relation to the way in which you referenced the Zhang et al study. If not, can you explain why not. If a phone call is possible some time today, let me know and what number to call you on. Many thanks and best wishes, Fiona

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On Tue, Apr 22, 2014 at 1:23 PM, Abramson, John David <John_Abramson@hms.harvard.edu> wrote:

From: Fiona Godlee[SMTP:FGODLEE@BMJ.COM]
Sent: Tuesday, April 22, 2014 1:23:09 PM
To: Abramson, John David
Cc: Trevor Jackson; Helen Macdonald
Subject: Re: Recent BMJ articles on statin safety and efficacy
Auto forwarded by a Rule
Dear John, Just to follow up on my earlier email.

I have had a closer look at Rory's specific complaint and have compared what you said about the Zhang et al paper with what the Zhang et al paper reports.

I don't think there is any problem with the figure of 18% that you quote, nor indeed the rounding up of the figure to 20% in the summary box. The Zhang paper uses the phrase "nearly 18%" in the text and rounds this up to "approximately one fifth" in the summary box.

But I do think the sentence in your paper is incorrect in that not all those who reported statin related adverse events discontinued therapy as a result.

You say

"A retrospective cohort study found that 18% of statin treated patients had discontinued therapy (at least temporarily) because of statin related adverse events."

Based on my reading of the Zhang paper I think it would be accurate to say
"A retrospective cohort study found that nearly 18% of statin treated patients had a statin related event. The authors concluded that as many as 87% of these patients discontinued treatment at least temporarily as a result."

If you agree, I would like us to publish a correction to this effect. It is a small point but better to address it straight up in my view, and move on to the much more important issues around access to the data, than allow this to become the focus of attack.

I would welcome a speedy response from you if at all possible.

With many thanks and all best wishes, Fiona

PS: I note that Rory is wrong in his letter about the definition of statin related adverse events, which are defined in the Zhang paper as "clinical events or symptoms documented by health care providers as having been caused by a statin."

Fiona Godlee
Editor in Chief

Re: FW: Recent BMJ articles on statin safety and efficacy

Inbox x

john Abramson 22 Apr

to me, Harriet, Nicholas, Jim, jay, Peter

Dear Fiona,
Given the default ("no longer necessary") in the EMR relied upon in the Zhang study, I am in complete agreement with your proposed correction:
"A retrospective cohort study found that nearly 18% of statin treated patients had a statin related event. The authors concluded that as many as 87% of these patients discontinued treatment at least temporarily as a result."

Much thanks for you close read of the Zhang paper and consideration of the statin transparency piece,
John

On 23 April 2014 09:12, Fiona Godlee <fgodlee@bmj.com> wrote:
Dear John. Below is the text of the correction to be published on Friday. Please let me have any comments before then. Best wishes. Fiona

Correction to article by Abramson et al

In referring to an observational study of patients taking statins, an article by Abramson et al [ref] said that 18% of patients discontinued therapy (at least temporarily) because of statin related adverse events. This was incorrect. The study, by Zhang et al, reported that "nearly 18%" of patients had a statin related event. The authors concluded that "as many as 87%" of these patients discontinued treatment at least temporarily as a result.[ref Zhang et al]

From: Fiona Godlee[SMTP:FGODLEE@BMJ.COM]
Sent: Wednesday, April 23, 2014 2:18:40 PM
To: Abramson, John David
Cc: Trevor Jackson; Helen Macdonald; Karl Sharrock
Subject: Re: Correction to your article
Auto forwarded by a Rule

Dear John, I have looked again at the Zhang et al paper and realised that I got it wrong - it's a rather confusing account of a study! Below is the revised text of the correction. I have also shared this with Rory Collins and will finalise the text once I have heard back from you all. Best wishes, Fiona

Proposed correction to article by Abramson et al

In referring to an observational study of patients taking statins, an article by Abramson et al said that 18% of patients discontinued therapy at least temporarily because of statin related adverse events.[ref] This was incorrect. The study reported that 17.4% of patients had a statin related event documented, of whom 59.2% discontinued the statin at least temporarily.The authors of the study concluded that "as many as 87%" of these discontinuations could have been due to statin related events.[ref Zhang et al]

Fiona Godlee
Editor in Chief

Re: FW: Correction to your article

Inbox x

On Wed, Apr 23, 2014 at 2:18 PM, Abramson, John David <John_Abramson@hms.harvard.edu> wrote:

john Abramson 23 Apr

to me, Harriet, Nicholas, Jim

Dear Fiona,
I apologize for having bungled up the Zhang article in the text of our BMJ piece (the box at the end of the article made the point correctly). Hoping to avoid getting further into the weeds, we purposely stayed away from the issue of probable under-ascertainment of statin-related adverse events in the Zhang article. The frequency of events was gleaned from structured EMR entries and unstructured Dr.-Pt.narratives, which were unlikely to have specifically queried patients about potentially statin-related symptoms. Now that the confusion we created is being put under a microscope, we might as well add one more sentence (in bold below) that accurately describes the results of the study. So I humbly offer the following:

In referring to an observational study of patients taking statins, an article by Abramson et al said that 18% of patients discontinued therapy at least temporarily because of statin related adverse events.[ref] This was incorrect. The study reported that **overall 53% of patients discontinued statin therapy at least temporarily. Review of structured EMR entries and unstructured narratives from follow-up visits showed** that 17.4% of

patients**reported** a statin-related event, of whom 59.2% discontinued the statin at least temporarily. The authors of the study concluded that "as many as 87%" of these discontinuations could have been due to statin related events.[ref Zhang et al]

My addition doesn't necessarily clarify the issue, but makes it more accurate. Thoughts?
John

From: Fiona Godlee[SMTP:FGODLEE@BMJ.COM]
Sent: Thursday, April 24, 2014 3:35:40 AM
To: Abramson, John David
Cc: Harriet Rosenberg; Nicholas P. Jewell; Jim Wright
Subject: Re: Correction to your article
Auto forwarded by a Rule
Dear John, Can I just check something else. You say that the box at the end of the article made the point correctly. I am expecting Rory to come back and say that this was the most egregious error - putting "about 20%" as the rate of adverse effects in a high profile summary box. Was this figure based specifically on Zhang et al or on a general view from all the studies. If based on Zhang et al, why do you say that the statement was correct. Thanks for your help with this, to prepare me for the next blast from Rory. Best wishes, Fiona

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Re: FW: Correction to your article

Inbox x

john Abramson 24 Apr

to me

Dear Fiona,

The language from the box in our BMJ article:
"• The side effects of statins—including muscle symptoms, increased risk of diabetes (especially in women), liver inflammation, cataracts,
decreased energy, sexual dysfunction, and exertional fatigue—occur in about 20% of people treated with statins"

The one fifth number comes directly from the box in Zhang et al, the specific adverse effects come from the references in the body of the article.

The specific language from the box (pasted below) in Zhang et al reads:
"Approximately one fifth of these patients [all who had been started on a statin] had a statin-related event that may have prompted discontinuation."

The following is our proposed correction (slightly modified to include the issue of potential under-ascertainment of statin-related events):

In referring to an observational study of patients taking statins, an article by Abramson et al said that 18% of patients discontinued therapy at least temporarily because of statin related adverse events.[ref] This was incorrect. The study reported that overall 53% of patients started on statin therapy discontinued at least temporarily. Review of structured EMR entries and unstructured narratives from follow-up visits for patients (vulnerable to under-ascertainment of statin-related

symptoms) showed that 17.4% of patients reported a statin-related event, of whom 59.2% discontinued the statin at least temporarily. The authors of the study concluded that "as many as 87%" of these discontinuations could have been due to statin related events.[ref Zhang et al]

There is another, much larger issue lurking in the background. As I am sure you are aware, Dr. Collins accused our article and the BMJ of potentially contributing to loss of life resulting from statin discontinuation in the Guardian, March 21, 2014:

Doctors worrying about the safety of cholesterol-reducing statins are creating a misleading level of uncertainty that could lead to the loss of lives, according to one of the UK's leading medical academics.

Professor Sir Rory Collins, from Oxford University, said he believes GPs and the public are being made unjustifiably suspicious of the drug, creating a situation that has echoes of the MMR vaccine controversy.

The academic, one of the country's leading experts on the drug, is particularly unhappy with the British Medical Journal (BMJ), which has run well-publicised articles by two critics of statins that he argues are flawed and misleading.

"It is a serious disservice to British and international medicine," he said, claiming that it was probably killing more people than had been harmed as a result of the paper on the MMR vaccine by Andrew Wakefield. "I would think the papers on statins are far worse in terms of the harm they have done."

I certainly respect Dr. Collins' effort to make sure we have interpreted the Zhang article properly. At the same time I am struck by his not challenging the primary point of the article: our recalculation of CTT mortality rates to show there is no mortality benefit of statins for people with < 20% 10-year risk. I fear that this relatively minor correction will be used to discredit the whole article. Therefore, might it be possible to add that the mortality calculations have not been challenged by the CTT group in the process that led to this correction?

From: Fiona Godlee[SMTP:FGODLEE@BMJ.COM]
Sent: Thursday, April 24, 2014 1:31:01 PM
To: Abramson, John David
Subject: Re: Correction to your article
Auto forwarded by a Rule
Many thanks John. Yes I agree that it would be good to clarify the fact that the analysis re mortality benefit has not been challenged.

I am not sure I agree with your interpretation of the Zhang et al summary box, but the language is confusing and my own interpretation doesn't fit with the figures in the paper.

I read the text in the box as saying that more than half of all patients in the study discontinued treatment at some point. And approximately one in five "of these patients" - that's 20% of the more than 50% rather than 20% of the total - had a statin related event that may have prompted discontinuation.

But as I say, I have tried and failed to find the numbers to fit with "20% of more than 50%"

I would welcome any further thoughts.

Best wishes, Fiona

Sent from my iPad

Correction to your article (slow progress)

Inbox x

john Abramson 24 Apr

to me, Harriet, Nicholas, Jim

Dear Fiona,
I think you have it right: 57,292 out of 107,835 (53%) statin treated patients discontinued their statins at least temporarily during the eight year study. Statin related events were documented in 18,778 (17.4%) of the 107,835 patients in the study. Among the 18,778 who experienced a statin-related event, 11,124 discontinued statins at least temporarily. So among the 57, 292 who discontinued, 11,124 had experienced a statin-related event, i.e. "approximately one fifth".
Because of uncertainty about overuse of default categories of reasons for discontinuation in the EMR, Zhang et al say:

> Overall, as many as 87% of statin discontinuations among patients with documented statin-related events could have been due to these events.

This modification supports the language in Zhang's box: one fifth of the one half who discontinued did so because of statin-related events—approximately 10% of the cohort.
The fly in the ointment, however, is that Zhang et al apply the "up to 87%" modification (because of the imprecise categorization of reason for statin discontinuation in the EMR) to those with recorded statin events, but what about the same default disclaimer being applied to a significantly greater percentage of the 57, 292 patients who discontinued, but—due to under-ascertainment of statin-related events by the EMR retrieval process from unstructured routine follow-up notes—were not included in the 18,778 who discontinued because of a statin-related event?
So I offer a slight modification of the last iteration of the correction:

> In referring to an observational study of patients taking statins, an article by Abramson et al said that 18% of patients discontinued therapy at least temporarily because of statin related adverse events.[ref] This was incorrect. The study reported that overall 53% of patients started on statin therapy discontinued at least temporarily. Review of structured EMR categories and automated review of unstructured narratives from follow-up visits for patients (vulnerable to under-ascertainment of statin-related symptoms) in the EMR showed that 17.4% of patients reported a statin-related event, of whom 59.2% discontinued statin therapy at least temporarily. However, because of possible mis-categorization due to the default category reason for discontinuation of statin therapy in the EMR, the authors of the study concluded that "as many as 87%" of these discontinuations could have been due to statin related events. [ref Zhang et al] Thus rather than stating that 18% of patients discontinued statins at least temporarily because of statin-related adverse events, we should have stated that, according to the article by Zhang et al, up to 10 % discontinued statin therapy at least temporarily because of at least one statin-related event. However, we also should have added that the study did not

determine the extent of under-ascertainment of statin-related events in data gleaned from non-structured routine follow-up visits.
Most important, the primary finding in our article—that CTT data fail to show reduction in overall risk of mortality by statin therapy for people with <20% risk of CVD over the next 10 years—was not challenged in the process of communication about this correction.

I hope the above addresses the issues in a fair and balanced manner, and look forward to your thoughts,

John

Fwd: Correction: Current and hopefully final draft

Inbox x

john Abramson 5 May (8 days ago)

to me, Harriet, Nicholas, Jim

Dear Fiona,
We have done our best to make sure the facts of the Zhang article are properly stated, our correction is clearly stated, and the ambiguities that remain are explained. We hope that, as you review the attached correction, you agree it fulfills these goals. Of course, we are open to further suggestions.
Sincerely,
John

ATTACHMENT TO ABOVE EMAIL DATED 5 MAY
In our article, we noted that side effects of statins occur in about 20% of patients. This statement

was based on an observational study by Zhang et al., which found that statin-related events had been

documented in the EMR of 17.4% of the more than 100,000 patients followed for 8 years. However,

in the text of our article we incorrectly referenced the study, saying that 18% of patients discontinued

therapy at least temporarily because of statin related adverse events. We withdraw this statement.

The Zhang et al. study reported that overall 53% of patients who started on statin therapy discontinued

at least temporarily. Review of structured EMR categories and automated review of unstructured

narratives from follow-up visits showed that of the 17.4% of patients who reported a statin-related

event (about 40% of which were musculoskeletal-related), 59.2% discontinued statin therapy at

least temporarily. Because of possible mis-categorization due to the default category reason for discontinuation of statin therapy in the EMR, the authors of the study concluded that "as many as 87%" of these discontinuations could have been due to statin related events. This equates to 9% of the study population having discontinued statins as a consequence of drug-related adverse events.

The authors of the study stated that “the rate of reported statin-related events to statins was nearly 18%, substantially higher than the 5% to 10% usually described in randomized, placebo-controlled, clinical trials.” However, two caveats must be considered: As Zhang et al. point out, the rate of statin-related events reported in their observational study was uncontrolled, and therefore may be inflated because events attributed to statins might have occurred in a placebo group as well. On the other hand, because of potential under-ascertainment of statin-related events in the unstructured interviews of the 53% of people in the study who discontinued statins, and other factors including the absence of some laboratory data, we believe this is likely to underestimate the overall rate of statin related adverse events.

The exact rate of statin related adverse events in people at low risk of cardiovascular disease remains uncertain. As discussed by Zhang et al, clinical trials may underestimate the frequency of statin-related adverse events due to patient selection, exclusion of older patients and those with comorbid conditions, underrepresentation of women, and selection bias created by willingness to participate in a clinical trial. Access to the full clinical study reports from the trials of statins would help to determine the comparative rates of serious adverse events in statin and control groups, but probably would not help to determine the frequency of less-than-serious statin-related adverse events.

We note that the primary finding in our article—that CTT data fail to show reduction in overall risk of mortality by statin therapy for people with <20% risk of CVD over the next 10 years—was not challenged

in the process of communication about this correction.

Re: Correction: Current and hopefully final draft

Fiona Godlee <fgodlee@bmj.com> 6 May

to john, Harriet, Nicholas, Jim, Helen, Trevor, Karl

Dear John, Many thanks. I am happy except for the first para. Painful as it is, you do need to withdraw the statement that side effects occur in nearly 18% of people taking statins (stated in your conclusion) and in about 20% (stated in the summary box). These statements are presented as matters of fact and can only be based on the Zhang et al paper since you reference no other. You say in the draft correction that you believe Zhang et al's numbers to be an underestimate. That is your opinion, which you entitled to have, but it is not based in fact. I am certain that it will be better to cleanly withdraw this statement and then rebuild your argument, which I am happy to give you space to do, rather than attempt to fudge matters. I will not pass this version on to peer reviewers until I have heard back from you. I would be grateful if you could get back to me with a further revision, withdrawing the overall statement on rate of side effects, before close of play today. Best wishes, Fiona

Correction (revised)

Inbox x

john Abramson 6 May (7 days ago)

to me, Harriet, Nicholas, Jim

Dear Fiona,
Once again, I am sorry that our correction has taken up so much of your time. The updated proposed correction (pasted below) I believe separates fact from opinion, and leads with a paragraph that clearly states the error that requires correction.
Please note the similarity between the language used by Zhang et al:
“The rate of reported statin-related events to statins was nearly 18%...”
And the language used in our BMJ article:
"Statin therapy...has about an 18% risk of causing side effects that range from minor and reversible to serious and irreversible.”
The quote from Zhang et al is also what we relied upon for our boxed statement:
"The side effects of statins...occur in about 20% of people treated with statins."
I fear that there is an issue here that we are not understanding. If so, perhaps a telephone conversation would be the quickest way to resolve this.
Sincerely,
John

CORRECTION:

In our article, we mistakenly reported that the observational study by Zhang et al found that "18% of statin treated patients had discontinued therapy (at least temporarily) because of statin-related events." This statement is not correct and we withdraw it.

Based on review of structured EMR categories and automated review of unstructured narratives from follow-up visits of 107 835 patients over 8 years, Zhang et al found that "Of all study patients, 18 778 (17.4%) had a statin-related event documented during the study." Further, among those who experienced a statin-related event, 59.2% had statin therapy discontinued at least temporarily. However, because of possible mis-categorization due to the limited options in the EMR listed as reasons for discontinuation of statin therapy, the authors of the study concluded that "as many as 87%" of these discontinuations could have been due to statin-related events. This equates to up to 9% of the study population (rather than the 18% we cited) having possibly discontinued statin therapy as a consequence of drug-related adverse events.

In our BMJ article, we stated that statin therapy "has about an 18% risk of causing side effects that range from minor and reversible to serious and irreversible." This statement was based upon Zhang et al's statement that "The rate of reported statin-related events to statins was nearly 18%..." We also based the bullet point in the box at the end of our article ("The side effects of statins…occur in about 20% of people treated with statins") on Zhang et al's report that nearly 18% of people followed in their study experienced statin-related events.

Zhang et al observed that the rate of statin-related events found in their study (18%) was "substantially higher than the 5% to 10% usually described in randomized, placebo-controlled, clinical trials." Two caveats must be considered: As Zhang et al. point out, the rate of statin-related events reported in their observational study was uncontrolled, and therefore may be inflated because events attributed to statins might have occurred in a placebo group as well. On the other hand, because of potential under-ascertainment of statin-related events in the unstructured interviews of the 53% of people in the study who discontinued statins, we believe (although this does not mitigate our incorrect statement described above) that, had follow-up interviews been structured to query specifically about potential statin-related events, the incidence of such events and discontinuation of statin therapy because of such events would have been higher than was found based on unstructured interviews.

The exact rate of statin related adverse events in people at low risk of cardiovascular disease remains uncertain. As discussed by Zhang et al, clinical trials may underestimate the frequency of statin-related adverse events due to patient selection, exclusion of older patients and those with comorbid conditions, underrepresentation of women, and selection bias created by willingness to participate in a clinical trial. Access to the full clinical study reports from the trials of statins would help to determine the comparative rates of serious adverse events in statin and control groups, but probably would not help to determine the frequency of less-than-serious statin-related adverse events.

We note that the primary finding in our article—that CTT data fail to show reduction in overall risk of mortality by statin therapy for people with <20% risk of CVD over the next 10 years—was not challenged in the process of communication about this correction.

Re: Correction (revised)

Fiona Godlee **<fgodlee@bmj.com>** 6 May

to john, Harriet, Nicholas, Jim

Many thanks John. I will take a good look and get back to you if any further clarification is needed before passing this on to our peer reviewers. I agree that the Zhang et al paper is far from easy to unpick and probably bears several different interpretations. Best wishes, Fiona

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From: Fiona Godlee[SMTP:FGODLEE@BMJ.COM]
Sent: Friday, May 09, 2014 7:43:42 AM
To: Abramson, John David
Cc: Harriet Rosenberg; Nicholas P. Jewell; Jim Wright
Subject: Re: Correction (revised)
Auto forwarded by a Rule
Many thanks John. I think it would be good to talk by phone today if possible. It is the main statements in the conclusions and summary box of your paper that I am asking you to withdraw - that side effects occur in 18-20% of people taking statins. This was based, as you say, on the statement in the Zhang paper but is stated as fact in your paper without necessary caveats and does not sufficiently take account of the uncontrolled nature of the data.

The other statement in the text needs correcting but is of less concern.

I should also make you aware of my plan for dealing with the rather problematic challenge we have received.

What number should I call you on and when would be good for you.

Best wishes. Fiona

Re: FW: Correction (revised)

On 9 May 2014, at 06:06 pm, john abramson <john_abramson@hms.harvard.edu<mailto:john_abramson@hms.harvard.edu>> wrote:

john Abramson 9 May (4 days ago)

to me, Harriet, Nicholas, Jim

Dear Fiona,
Best if we could talk. Briefly, the precise incidence of side effects (which we clearly need to correct) is secondary. Having shown no mortality benefit and no evidence of reduction of SAEs, then any amount of side effects attributable to statins tips the benefit/harm equation towards harm. Whether the true incidence of statin-related side effects is 5%, 10%, 20% or more is not the question--the balance of the equation remains the same.
So I think a correction is in order.
If Rory Collins feels that our citing of Zhang would leave a permanent false impression about evidence of side effects, and a correction attached to the paper is insufficient, then I would propose

that rather than retraction that we replace the current paper with a corrected version, with the first version no longer available on the web.
I think it would be a gross restriction of academic debate to withdraw the re-analysis of CTT data about mortality for people with less than 20% 10-year CV risk, and that a secondary error should not be used as an excuse to achieve that goal.
John

NOTE: FG & JA DID NOT SPEAK BY PHONE

From: Fiona Godlee[SMTP:FGODLEE@BMJ.COM]
Sent: Friday, May 09, 2014 12:47:44 PM
To: Abramson, John David
Cc: Harriet Rosenberg; Nicholas P. Jewell; Jim Wright; Helen Macdonald
Subject: Re: Correction (revised)
Auto forwarded by a Rule
Many thanks John. I have sent it for comments to Zhang et al and to the two reviewers of your paper. We are also looking into where in the process the summary box and the firm statement in the conclusions were introduced, since there may be lessons here for the journal, which we should acknowledge.

You should know that Rory Collins has renewed his call for the entire article to be retracted on the grounds that people will continue to cite it if we don't.

He has undertaken to summarise his concerns in writing, though still not for publication I'm afraid. I propose to convene an independent external panel to deliberate on this. I will be back in touch once I have heard back from the peer reviewers.

Best wishes. Fiona

Sent from my iPhone

On 9 May 2014, at 02:19 pm, john abramson <john_abramson@hms.harvard.edu> wrote:

Dear Fiona,
I understand the point you have been making about the statement in the box and agree with the changes you have made. I would propose the addition of one sentence-- highlighted below--that reflects the PLOS paper on lack of reporting of AEs when CSRs are compared to journal publications, as you pointed out in our last communication.
I am at my desk and available whenever it is convenient for you to call.
John

In our article, we stated that side effects of statins occur in about 18-20% of patients. We withdraw this statement. Although it was based on statements in the referenced paper by Zhang et al that "the rate of reported statin-related events to statins was nearly 18%," our article did not reflect necessary caveats and did not take sufficient account of the uncontrolled nature of the study. Zhang et al observed that the rate of statin-related events found in their study (18%) was "substantially higher than the 5% to 10% usually described in randomized, placebo-controlled, clinical trials." Three caveats must be considered: As Zhang et al point out, the rate of statin-related events reported in their observational study was uncontrolled, and therefore may be inflated because events attributed to statins might have occurred in a placebo group as well. In addition, although Zhang et al do not make this point, the 5-10% rate quoted by Zhang et al as having been observed in randomised trials was, in many cases, similar in both active and placebo groups. On the other hand, (notwithstanding the unresolved issue of potential lack of external validity of adverse event rates recorded in clinical trials discussed below), when compared to Clinical Study Reports, journal publications report only 21% of adverse events. [Wieseler B, Wolfram N, McGauran N, Kerekes MF,

Vervolgyi V, et al. (2013) Completeness of Reporting of Patient-Relevant Clinical Trial Outcomes: Comparison of Unpublished Clinical Study Reports with Publicly Available Data. PLoS Med 10(10): e1001526. doi:10.1371/journal.pmed.1001526]

The exact rate of statin related adverse events in people at low risk of cardiovascular disease remains uncertain. As discussed by Zhang et al, observational studies report rates of [add rates]. Meanwhile, clinical trials may underestimate the frequency of statin-related adverse events due to patient selection, exclusion of older patients and those with comorbid conditions, underrepresentation of women, and selection bias created by willingness to participate in a clinical trial. Access to the full data from the trials of statins would help to determine the comparative rates of serious adverse events in statin and control groups, but probably would not help to determine the frequency of less-than-serious statin-related adverse events.

Also in our article, we mistakenly said that Zhang et al found that "18% of statin treated patients had discontinued therapy (at least temporarily) because of statin-related events." Based on review of structured EMR categories and automated review of unstructured narratives from follow-up visits of 107 835 patients over 8 years, Zhang et al found that “Of all study patients, 18 778 (17.4%) had a statin-related event documented during the study.” Further, among those who experienced a statin-related event, 59.2% had statin therapy discontinued at least temporarily. However, because of possible mis-categorization due to the limited options in the EMR listed as reasons for discontinuation of statin therapy, the authors of the study concluded that "as many as 87%" of these discontinuations could have been due to statin-related events. This equates to up to 9% of the study population having possibly discontinued statin therapy as a consequence of drug-related adverse events, rather than the 18% we cited.

We note that the primary finding in our article—that CTT data fail to show reduction in overall risk of mortality by statin therapy for people with <20% risk of CVD over the next 10 years—was not challenged in the process of communication about this correction.

From: Fiona Godlee [fgodlee@bmj.com]
Sent: Friday, May 09, 2014 4:25 PM
To: Abramson, John David
Cc: Harriet Rosenberg; Nicholas P. Jewell; Jim Wright; Helen Macdonald
Subject: Re: Correction (revised)

Dear John. I am likely to take the same view. But as the editor who published the article, I have a vested interest in not retracting it. The panel will be made up of good people with the right expertise and no dog in this fight, and it will include someone experienced in distinguishing between the need for correction and the need for retraction. And you, as well as Rory Collins, will be able to put your case. I will also ask that the panel's deliberations are transparent, which will mean that Rory's submission will be published along with yours.

I hope this gives you a little reassurance. I will be back in touch when I have feedback on the correction.

Best wishes. Fiona

RE: Correction (revised)

Inbox x

Abramson, John David

9 May (4 days ago)

to me, Harriet, Nicholas, Jim, Helen

Dear Fiona,
It does reassure, and will offer an opportunity for a full airing of the issues.
Much thanks from all of us,
John

From: Emma Dickinson [edickinson@bmj.com<mailto:edickinson@bmj.com>]
Sent: Wednesday, May 14, 2014 10:12 AM
To: Abramson, John David; aseem malhotra
Cc: Fiona Godlee
Subject: Press release: BMJ authors withdraw statements about adverse effects of statins

Dear John / Aseem

Below is the press release that will be issued shortly - based on Fiona's editorial in this week's journal (there's a link to the full editorial at the end).

It's embargoed until just after midnight UK time tonight - when the full editorial / corrections will be published on bmj.com<http://bmj.com><http://bmj.com>

Fiona is happy to take calls from journalists today / tomorrow, but you may also want to prepare for calls.

If possible, could you both send me a contact number that I can give to journalists wishing to speak to you.

Many thanks
Emma

BMJ Press Release
Embargo 00:01 hours (UK time) Thursday 15 May 2014

BMJ authors withdraw statements about adverse effects of statins

Decision whether to retract articles will be made by an independent panel

Editorial: Adverse effects of statins

Authors of two articles published in The BMJ last year are withdrawing statements about the adverse effects of statins.

An editorial by Editor-in-Chief, Dr Fiona Godlee aims to alert readers, the media, and the public to the withdrawal of these statements “so that patients who could benefit from statins are not wrongly deterred from starting or continuing treatment because of exaggerated concerns over side effects.”

Dr Godlee has also asked an independent expert panel to decide whether the articles should be retracted.

In October last year, The BMJ published an article by John Abramson and colleagues that questioned the evidence behind new proposals to extend the routine use of statins to people at low risk of cardiovascular disease.

The authors re-analysed data from the Cholesterol Treatment Trialists’ (CTT) Collaboration and suggested that side effects of statins occur in 18-20% of people. This figure was repeated in another article published in the same week in The BMJ by Aseem Malhotra.

The BMJ was alerted to the error by Rory Collins, professor of medicine and epidemiology at Oxford University and head of the CTT Collaboration whose data were re-analysed by Abramson and colleagues.

This error was due to a misreading of data from one observational study, and was not picked up by the peer reviewers or editors, explains Dr Godlee. “The BMJ and the authors of both these articles have now been made aware that this figure is incorrect, and corrections have been published withdrawing these statements.”

She explains that writing, peer reviewing, and editing are human processes subject to error, “which is why we must be, and are, ready to correct things when they are found to be wrong.”

Professor Collins has requested retraction of both articles, but Dr Godlee questions whether the error is sufficient for retraction, “given that the incorrect statements were in each case secondary to the article’s primary focus.”

Guidelines of the International Committee on Publication Ethics state that journals should consider retracting a publication if there is clear evidence that the findings are unreliable, either as a result of misconduct or honest error.

Dr Godlee has decided to pass this decision to an independent panel, chaired by Iona Heath, former chairwoman of the Royal College of General Practitioners and of The BMJ’s ethics committee.

Full details of the panel and processes will be published shortly, and all submissions to the panel will be placed in the public domain on bmj.com<http://bmj.com><http://bmj.com/>. Dr Godlee has also committed to implementing the panel’s recommendations in full.

Meanwhile, she says, “The BMJ will continue to debate the important questions raised in both these articles: whether the use of statins should be extended to a vastly wider population of people at low risk of cardiovascular disease; and the role of saturated fat in heart disease.

Contact:
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Embargoed link to full editorial: http://press.psprings.co.uk/bmj/may/statins.pdf
Public link once embargo lifts: http://www.bmj.com/cgi/doi/10.1136/bmj.g3306

Emma Dickinson
Media Relations Manager

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rom: Emma Dickinson [edickinson@bmj.com]
Sent: Wednesday, May 14, 2014 11:19 AM
To: Abramson, John David
Cc: aseem malhotra; Fiona Godlee
Subject: Re: Press release: BMJ authors withdraw statements about adverse effects of statins

Thanks John. Revised version below (changes in red - OK)?

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Dr Godlee has also asked an independent expert panel to decide whether the articles should be retracted.

In October last year, The BMJ published an article by John Abramson and colleagues that questioned the evidence behind new proposals to extend the routine use of statins to people at low risk of cardiovascular

disease.

The authors re-analysed data from the Cholesterol Treatment Trialists' (CTT) Collaboration. This showed no mortality benefit associated with treatment of people with a less than 20% risk of developing cardiovascular disease over the next 10 years. This has not been challenged.

However, they also cited data from a separate uncontrolled observational study showing that statin side effects occur in 18-20% of patients. This was repeated in another article published in the same week in The BMJ by Aseem Malhotra – and is the statement the authors have now withdrawn.

The BMJ was alerted to the error by Rory Collins, professor of medicine and epidemiology at Oxford University and head of the CTT Collaboration whose data were re-analysed by Abramson and colleagues.

This error was due to a misreading of data from one observational study, and was not picked up by the peer reviewers or editors, explains Dr Godlee. "The BMJ and the authors of both these articles have now been made aware that this figure is incorrect, and corrections have been published withdrawing these statements."

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Meanwhile, she says, "The BMJ will continue to debate the important questions raised in both these articles: whether the use of statins should be extended to a vastly wider population of people at low risk of cardiovascular disease; and the role of saturated fat in heart disease.

Contact:
Fiona Godlee, Editor-in-Chief, BMJ, London, UK
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Embargoed link to full editorial: http://press.psprings.co.uk/bmj/may/statins.pdf
Public link once embargo lifts: http://www.bmj.com/cgi/doi/10.1136/bmj.g3306

Emma Dickinson
Media Relations Manager

On 14 May 2014 15:21, Abramson, John David <John_Abramson@hms.harvard.edu<mailto:John_Abramson@hms.harvard.edu>> wrote:
Dear Emma and Fiona,

I believe the following sentence from the press release is not quite correct:

"The authors re-analysed data from the Cholesterol Treatment Trialists' (CTT) Collaboration and suggested that side effects of statins occur in 18-20% of people."

Our re-analysis of the CTT data showed that there is no mortality benefit associated with treatment of

people whose risk of ASCVD is < 20% over the next 10 years. This has not been challenged. Our error was in the citing of data from a completely separate uncontrolled observational study as showing that statin side effects occur in 18-20% of patients. This is the statement we withdraw.

Is it possible to have both of these points clarified in the press release?

Much thanks,
John

RE: Press release: BMJ authors withdraw statements about adverse effects of statins

Inbox x

Abramson, John David 14 May (5 days ago)

to Emma, aseem, me

Emma,
Yes, changes in red are accurate. Thanks to you and Fiona for the quick response. The best way for journalists to contact me is at this email address and on my cell phone.
Sincerely,
John

Re: Press release: BMJ authors withdraw statements about adverse effects of statins

Inbox x

Emma Dickinson 14 May (6 days ago)

to John, aseem, me

Wonderful, thanks for your help. Will get this out now.
Emma

Emma Dickinson

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http://company.bmj.com/content/bmj-authors-withdraw-statements-about-adverse-effects-statins