

RESPONSE TO THE LETTER OF COMPLAINT TO THE COMMITTEE ON PUBLICATION ETHICS BY PROF. COLLINS ET AL

We would like to thank Prof. Collins et al for the opportunity to respond to their ethics complaint regarding our BMJ article of October 2014.¹ First Prof. Collins et al state that in the section of our paper titled “Myopathy,” we “misleadingly compared” the rates of myopathy (as defined by CTT) to the rates of musculoskeletal symptoms reported in the NHANES observational study, “which did not assess myopathy” and which “had no ‘blinded’ comparator group.” Second, Prof. Collins et al raise concern about our having failed to respond to an “error” in our original manuscript that had been pointed out by a peer reviewer: that the frequency of musculoskeletal symptoms reported in the manuscript was “misleading” because only musculoskeletal symptoms among statin users were ascertained, without taking into account the fact that “muscle pain is incredibly common in the general population.” And finally, Prof. Collins et al state that in response to Cochrane Collaboration statin trial reviewers’ Rapid Response, which expressed concern about our use of the term “myopathy,” the BMJ allowed us “to repeat our misleading claim.”

None of these statements about the article as published in the BMJ or our response to the Cochrane Collaboration statin trial reviewers is correct.

Addressing the first issue, Prof Collins et al wrote in their complaint that, under the heading of “Myopathy,” we had “misleadingly compared” the rate of statin-associated myopathy reported in the CTT meta-analyses “(i.e. a severe muscle problem with a specific definition)” to the rate of more common statin-associated musculoskeletal symptoms based on the NHANES survey as reported by Buettner et al² “(which did not assess myopathy)”.

Notwithstanding the opinion of Prof. Collins et al about what the definition of myopathy should be, there is not one universally accepted definition. We relied upon the approach taken by Fernandez et al in the Cleveland Clinic Journal of Medicine, titled “Statin myopathy: A common dilemma not reflected in clinical trials,”³ cited as footnote 11 in our Rapid Response of 20 December 2013. This article acknowledges that “little consensus exists on how to define the adverse muscle effects of statins, which may contribute to the under-diagnosis of this complication.” The authors define three categories of statin-induced myopathy: myalgia (muscle symptoms without elevation of CK enzyme), myositis (elevated CK with or without muscle symptoms), and rhabdomyolysis (muscle symptoms with CK level ≥ 10 times the upper limit of normal). These authors’ broad definition of myopathy is clear in the following excerpt:

Another reason [statin-induced myopathy is so uncommon in clinical trials] is that these trials were designed to assess the efficacy of statins and were not sensitive to adverse effects like muscle pain. When they looked at myopathy, they focused on

¹ Abramson J, Rosenberg H, Jewell N, Wright JM, Should people at low risk of cardiovascular disease take a statin? *BMJ* 2013;347:f6123 doi: 10.1136/bmj.f6123 (Published 22 October 2013, Correction May 15, 2014)

² Buettner C, Davis RB, Leveille SB, et al, Prevalence of Musculoskeletal Pain and Statin Use, *J Gen Intern Med*, 2008; 23:1182–6

³ Fernandez G, Spatz ES, Jablecki C, Phillips PS, Statin myopathy: A common dilemma not reflected in clinical trials, *Cleveland Clinic Journal of Medicine*, 2011;78:393-403

rhabdomyolysis—the most severe form—rather than on myalgia, fatigue, or other minor muscle complaints.

This broader definition of “myopathy” is consistent with that presented in the 2002 American College of Cardiology/American Heart Association/National Heart, Lung, and Blood’s “Clinical Advisory on the Use and Safety of Statins.”⁴ Focusing specifically on the use of the term “myopathy,” this document states that because the terminology describing muscle toxicity was inconsistent, it would provide more specific definitions. “Myopathy” was then defined as “a general term referring to any disease of muscles.” Under the general heading of myopathy, the document identified three subcategories of muscle problems:

- Myalgia—muscle ache or weakness without creatine kinase (CK) elevation.
- Myositis—muscle symptoms with increased CK levels.
- Rhabdomyolysis—muscle symptoms with marked CK elevation (typically substantially greater than 10 times the upper limit of normal [ULN]) and with creatinine elevation (usually with brown urine and urinary myoglobin).

The Canadian Working Group on statin adverse events and intolerance also chose to adopt the broad definition of myopathy as a collective term encompassing all forms muscle disease:⁵

The term does not necessarily connote symptoms or any degree of CK elevation. For example, several myopathies may present with normal CK levels, including steroid myopathy, critical-illness myopathy, pediatric dermatomyositis, myotonic dystrophy type 2, and the periodic paralyses. Indeed, biopsy evidence suggests that even some statin induced myopathic changes may be present in the context of normal CK levels.

On the other hand, the CTT as well as the National Lipid Association and the FDA, have chosen to define myopathy as having muscle symptoms *and* CK levels > 10 times the upper limit of normal. This measure of a statin-induced muscle problem is limited to significant muscle inflammation, a small subset of the broader category of statin-related muscle problems. Which of the two definitions is most relevant is a matter of opinion, but use of one definition or the other is neither factually wrong nor misleading.

The external panel appointed by The BMJ to determine whether retraction of our article was warranted, wrote this about our use of term “myopathy”:

The panel thought that including three different definitions of muscle problems, widely ranging in severity, all under a heading of the more serious myopathy, might lead to the reader to conflate these. However, as Abramson et al point out in their submission to the panel (SP23), myopathy and myalgia can be conflated in the opposite direction by referring to severe problems as if they included milder ones and this can also lead to misinterpretation.

⁴ Pasternak RC, Smith SC, Bairey-Merz CN, et al., ACC/AHA/NHLBI Clinical Advisory on the Use and Safety of Statins, *Circulation* 2002;106:1024-1028.

⁵ Mancini GBJM, Baker S, Bergeron J, et al., Diagnosis, Prevention, and Management of Statin Adverse Effects and Intolerance: Proceedings of a Canadian Working Group Consensus Conference, *Canadian Journal of Cardiology*, 2011; 27: 635–662.

The frivolous nature of the ethics complaint by Prof. Collins et al about our reporting multiple types of statin-related muscle symptoms under the single heading of “Myopathy” is made clear in Prof. Collins’ citation of a 2014 article in his request for retraction of our BMJ article.⁶

These carefully conducted randomised trials and meta-analyses of trials (along with meta-analyses of relevant observational studies; for example, Macedo et al; *BMC Medicine* 2014)...

Four out of five of the authors of the article by Macedo et al are members of the Cochrane Heart Group.⁷ Under the heading titled “Myopathy,” this article includes multiple definitions of muscle problems associated with statin use: an increased odds ratio of myopathy with no definition, a significant decrease in grip strength associated with statin therapy in both men and women,⁸ CTT’s finding of increased risk of myopathy (without definition), and the results of an observational study showing that the prevalence rate of any myopathic event (which used the ACC/AHA/NHLBI definition described above⁹) associated with statin initiation is approximately 250 such events per 10,000 person years. Although not stated in the article by Macedo et al, 95% of the myopathic events reported in this last study were either myalgia or myositis,¹⁰ not meeting the CTT’s criteria for myopathy.

In retrospect, had we stated explicitly that we were using the broader definition in the “Myopathy” section of our paper, this confusion would have been avoided. But our comparison of the rates of myopathy as defined by CTT (symptoms plus CK levels > 10 times normal) to the absolute increase in the number of statin-users vs. non-users experiencing musculoskeletal symptoms would not have changed. However, it should be noted that neither the 2012 nor 2015 CTT meta-analyses state that their definition of “myopathy” is limited to people with muscle symptoms plus enzyme elevations (this definition is relegated to a footnote). Although we think the CTT’s approach minimizes the frequency with which people treated with statins experience muscle symptoms, we do not feel that this warrants a letter of complaint about the Lancet’s CTT publications to the Committee on Publication Ethics.

Addressing the second issue, Prof Collins et al state that we failed to respond to a peer reviewer’s comment that the results from the NHANES study in our manuscript were misleading because (in essence) we presented uncontrolled data on the rate of musculoskeletal symptoms reported by statin users in the NHANES survey. Had this data been uncontrolled, Prof. Collins et al would have been correct that it was meaningless because musculoskeletal symptoms are so

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<http://journals.bmj.com/site/bmj/statins/SP15%20Note%20from%20Rory%20Collins%20for%20the%20panel%20considering%20the%20retraction%20of%20Abramson%20and%20Malhotra%20papers.pdf>
Accessed April 12, 2015

⁷ Unintended effects of statins from observational studies in the general population: systematic review and meta-analysis, *BMC Medicine*, 2014;12:51. <http://www.biomedcentral.com/1741-7015/12/51>
Accessed April 12, 2015.

⁸ Ashfield TA, Syddall HE, Martin HJ, et al, Grip strength and cardiovascular drug use in older people: findings from the Hertfordshire Cohort Study. *Age Ageing* 2010, 39:185–191.

⁹ Nichols GA, Koro CE: Does statin therapy initiation increase the risk for myopathy? An observational study of 32,225 diabetic and nondiabetic patients. *Clin Ther*, 2007, 29:1761–1770.

¹⁰ *Ibid.*

common in the general population. However, in order to determine the “muscle effects” of statins, Buettner et al¹¹ used the NHANES database to compare the prevalence of any musculoskeletal pain in statin users and non-users among a sample of 3,580 adults ≥ 40 years of age.

In response to the peer reviewer’s comment, we wrote to BMJ editors:

The NHANES data [were] not simply the incidence of muscle pain in statin-takers, but the difference in prevalence of muscle pain between statin takers and non-statin takers, so this should be an accurate reflection of the effect [of] statins on the prevalence of muscle pain. This was clarified in the updated manuscript.

Based on the reviewer’s comment, we revised the language in the published article to clarify that the NHANES data did not simply reflect the background incidence of muscle pain in statin users, but rather the authors compared the prevalence of muscle symptoms in statin users and non-users.

Finally, the ethics complaint by Prof. Collins’ et al states that when Cochrane Collaboration statin trial reviewers pointed out our “error” conflating myopathy (per the definition adopted by CTT) with the broader category of statin-related muscle problems (described above) in Rapid Response letters, “the BMJ allowed Abramson et al to repeat their misleading claim instead of correcting it.”

The Cochrane reviewers letter stated:¹²

They also conflate muscle pain (myalgias), an important side effect of statins, with myopathy, a rare and more serious problem, both of which warrant ongoing study.

We responded:¹³

This is a semantic criticism, with which we disagree. From a practical point of view, statin induced myopathy includes: myalgia (muscle symptoms without raised creatine kinase), myositis (raised creatine kinase, with or without muscle symptoms), and rhabdomyolysis (creatinine >10 times the upper limit of normal).¹⁴ Furthermore, histopathological findings of myopathy occur in patients with or without muscle symptoms and normal creatine kinase levels.^{15 16 17}

¹¹ Buettner et al, *op.cit.*

¹² *BMJ* 2014;348:g1520

¹³ *BMJ* 2014;348:g1523

¹⁴ Fernandez G, Spatz ES, Jablecki C, Phillips PS, Statin myopathy: A common dilemma not reflected in clinical trials, *Cleveland Clinic Journal of Medicine*, 2011;78:393403

¹⁵ Draeger A, Monastyrskaya K, Mohaupt M, et al, Statin therapy induces ultrastructural damage in skeletal muscle in patients without myalgia, *Journal of Pathology*, 2006; 210: 94–102.

¹⁶ Association between statin-associated myopathy and skeletal muscle damage, *Canadian Medical Association Journal*, 2009;181(12):E11E18.

¹⁷ Phillips PS, Haas RH, Bannykh S, et al, Statin Associated Myopathy with Normal Creatinine Kinase Levels, *Annals of Internal Medicine*, 2002;137:581585

Ironically, two of the three Cochrane reviewers who submitted the Rapid Response in question were co-authors on the paper by Macedo et al , whose section titled “Myopathy” didn’t only conflate myalgias with myopathy, but also failed to inform readers which definition pertained to which findings.

The external panel appointed to adjudicate Prof. Collins’ request for retraction of our BMJ article did not find fault with either the editors’ selection of Rapid Responses sent to us, or with our replies:

Rapid responses

Assessment

The journal received several rapid responses that raised substantive criticisms and discussion of the Analysis article. The editors’ selections of rapid response letters that were directed to John Abramson for further response and discussion were appropriate. Editors’ decision-making about those selections and their follow-up was executed in a timely manner. John Abramson and colleagues responded to the selected letters promptly.

In conclusion, we do believe there is an important ethical issue raised by our article and The BMJ’s editorial decisions related to our article. The unrelenting harassment we have been subjected to by Prof. Collins—in the media, in the demand for retraction of our paper that was unanimously rejected by the external panel (with Prof. Collins having been unwilling to make public the concerns he expressed to The BMJ about our paper prior to the panel’s decision), and now through a letter of complaint to the Committee on Publication Ethics about The BMJ’s handling of our article—is creating an atmosphere in which responsible scientific discourse is being strongly discouraged. Specifically, these ongoing tactics are inimical to improving our understanding of the benefits and risks of statins. If this process is allowed to continue or be repeated, a great disservice will be done to the public.

John Abramson, Harriet Rosenberg, Nicholas Jewell, J M Wright

(John Abramson and Nicholas Jewell serve as experts in litigation, including cases involving statins)