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### **Response to Letter to the Editor re: "Serious adverse events and deaths in PCSK9 inhibitor trials reported on ClinicalTrials.gov: a systematic review"**

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LETTER TO THE EDITOR



## Response to letter to the editor re: 'serious adverse events and deaths in PCSK9 inhibitor trials reported on ClinicalTrials.gov: a systematic review'

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Our review of PCSK9 inhibitor trials was based on data that is publicly available on ClinicalTrials.gov [1]. The FDA Amendments Act mandates submission of trial results on this website in reaction to numerous examples of selective reporting and the cover-up of potentially harmful drug effects [2–4]. All serious diseases that occurred should be reported under the heading Serious Adverse Events (SAE), and all deaths under the heading All-cause Mortality. It must be remembered that trial investigators need to ensure that the submitted data are accurate and complete [5].

Sabatine and colleagues [6] raise concerns about the validity of the data that we used. They claim that adjudicated cases of myocardial infarction (MI) and stroke in FOURIER and ODYSSEY OUTCOMES have not been posted under the heading SAE. If true, this is indeed reason for concern. MI and stroke are SAE and need to be reported as such, whether they are prespecified and adjudicated diseases or not. A problem is also that the high number of unstable anginas posted under the heading SAE for FOURIER suggests that this prespecified, adjudicated event was reported as required. Such inconsistent reporting would fundamentally undermine the usefulness of the SAE data.

Moreover, if the posted MIs and ischemic strokes are unconfirmed events, the numbers question the objectivity of the adjudication process. The variation in the proportion of such events across studies should not be as high as it was: for MI 8% in FOURIER and 1% in ODYSSEY OUTCOMES, and for stroke 17% and 2%, respectively. Even more worrying would be that the proportion of unconfirmed strokes was higher in the drug group than the placebo group of FOURIER (21% and 14%;  $p = 0.044$ ) and ODYSSEY OUTCOMES (3% and 1%;  $p = 0.231$ ).

Sabatine and colleagues also denounce our low rates of MI and stroke/TIA per year. However, the absolute numbers of events that they cite do not contradict these rates per se. The events occurred in very large study populations during multiple years of follow-up. In fact, only supersized trials will yield a statistically significant result if the absolute treatment effect is really small, perhaps even clinically insignificant [6,7]. According to published results, MI was prevented in 1.2% of patients treated with evolocumab for 2.2 years, and in 1.1%

treated with alirocumab for 2.8 years [8,9]. Stroke was prevented in 0.4% of patients in both scenarios. The FDA and EMA have not appraised the clinical relevance of the drug effects – they seldom do. The industry funded European Society of Cardiology and European Atherosclerosis Society may not provide an independent guideline [10,11]. Many of their guideline developers received personal funding of Amgen and Sanofi [12].

Next, Sabatine and colleagues criticize the risks of all-cause mortality that we reported, asserting that we presented odds ratios in time-to-event analyses. However, we calculated pooled odds ratios with numbers of deaths in the comparison groups, which is common in meta-analyses. They further assume that the numbers of deaths that we used are incorrect, even though the numbers were based on the posted data. We urge the investigators to clear up the apparent confusion and provide the required information unequivocally and transparently on ClinicalTrials.gov. We would be very willing to reanalyze the risk of death.

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### Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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