Health inequalities in the UK

Your Nov 13 Editorial (p 1617),[1] which accuses the negotiators of the UK's general practitioner (GP) contract of sharing a responsibility for deaths as a result of health inequalities, is not only wrong and grossly insulting, it betrays a worrying lack of knowledge about the nature of health inequalities and how to tackle them.

You say that "there are some simple and proven interventions that, if implemented evenly across the population, would go a long way to reduce inequalities in health—notably, smoking cessation and the treatment of high blood pressure and raised cholesterol." That is exactly what the Quality and Outcomes Framework (QOF—a key component of the new GP contract) does. Evidence published in *The Lancet* in 2008[2] showed that the QOF was reducing inequity in health care. A more recent study[3] found that the QOF has had a demonstrable effect on outcome indicators such as heart attacks and deaths; the effect was strongest in practices in the most deprived areas, which had more than twice the reduction in admissions and deaths from coronary heart disease. Other studies[4] highlight the positive effect the QOF is having on chronic disease, which tends to be more prevalent in socially deprived areas, both in terms of the quality of health care delivered and the outcomes experienced by patients themselves. And there is evidence[5] that the QOF has raised the potential of primary care to reduce hospital admissions, something else which also tends to be higher in socially deprived areas.

The QOF was always intended to have a positive effect on public health over the long-term, and we expect that the true gains will be seen even more clearly as the evidence base develops. The British Medical Association (BMA) negotiators who worked on the GP contract feel very proud to have been involved in producing something that, through its focus on prevention rather than cure, has saved lives and improved the quality of many more.

In your attempt to attack the GP contract and its negotiators, you have lost sight of what really matters—continuing action on and debate about how we can improve equality in health. In his report for government, *Fair Society, Healthy Lives*, the current BMA President Michael Marmot argues that social inequalities are the greatest contributors to health inequalities. His report says that reducing health inequalities requires action across a wide range of policies, one of which is ill-health, and called for co-ordinated action by central and local government, the National Health Service, the third and private sectors, and community groups. GPs can—and are—working hard to manage the effects of these, but we alone cannot rectify the causes. Your Editorial did the 45 000 GPs in the UK a great disservice and we believe you owe them an apology.

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1 The Lancet. "Claptrap" from the UK's Department of Health. *Lancet* 2010; **376:** 1617.
2 Doran T, Fullwood C, Kontopantelis E, Reeves D. Effect of financial incentives on inequalities in the delivery of primary clinical care in England: analysis of clinical activity indicators for the quality and outcomes framework. *Lancet* 2008; **372:** 728–36.
3 Kiran T, Hutchings A, Dhalla I A, Furlong C, Jacobson B. The association between quality of primary care, deprivation and cardiovascular outcomes: a cross-sectional study using data from the UK Quality and Outcomes Framework. *J Epidemiol Community Health* 2010; **64:** 927–34.
4 Khunti K, Gadsby R, Millett C, Majeed A, Davies M. Quality of diabetes care in the UK: comparison of published quality-of-care reports with results of the Quality and Outcomes Framework for Diabetes. *Diabet Med* 2007; **24:** 1436–41.
5 Downing A, Rudge G, Cheng Y, Tu YK, Keen J, Gilthorpe MS. Do the UK government's new Quality and Outcomes Framework (QOF) scores adequately measure primary care performance? A cross-sectional survey of routine healthcare data. *BMC Health Serv Res* 2007; **7:** 166.

Termination of the CRESCENDO trial

The CRESCENDO trial of rimonabant (Aug 14, p 517)[1] confirmed the conclusions of previous meta-analyses: rimonabant increases the risk of serious adverse events with no evidence of benefit on major cardiovascular outcomes.[2-4] According to Eric Topol and colleagues,[1] the trial was stopped prematurely because "the level of serious neuropsychiatric effects was deemed unacceptable by regulatory authorities". We argue that the trial was terminated too late, not too soon.

First, CRESCENDO began months after the marketing approval for rimonabant as a weight-loss drug had been requested in Europe. Testing the efficacy of a drug on hard outcomes after its marketing for uncertain surrogates is a time sequence in the interest of the manufacturer, not of public health.

Second, the marketing approval for rimonabant was issued by the European Commission in June, 2006, but withdrawn in November, 2008.[5] However, concerns about an unfavourable benefit-risk balance of rimonabant had already been expressed in 2006, shortly after the marketing approval was granted.[3] Rimonabant was never marketed in the USA because the application was rejected by the Food and Drug Administration in 2007[4] (figure). Thus the European Medicines Agency was indeed rather slow in cancelling the marketing approval, and when it did so, it was on the basis of strong evidence and not of "concerns", as suggested by Topol and colleagues.

Finally, there is no evidence that a longer duration of CRESCENDO would have shown rimonabant's benefits. Even with 12 190 and 5092 participants at year 1 and year 2, respectively, not the slightest divergence in survival curves between groups could be detected—in sharp

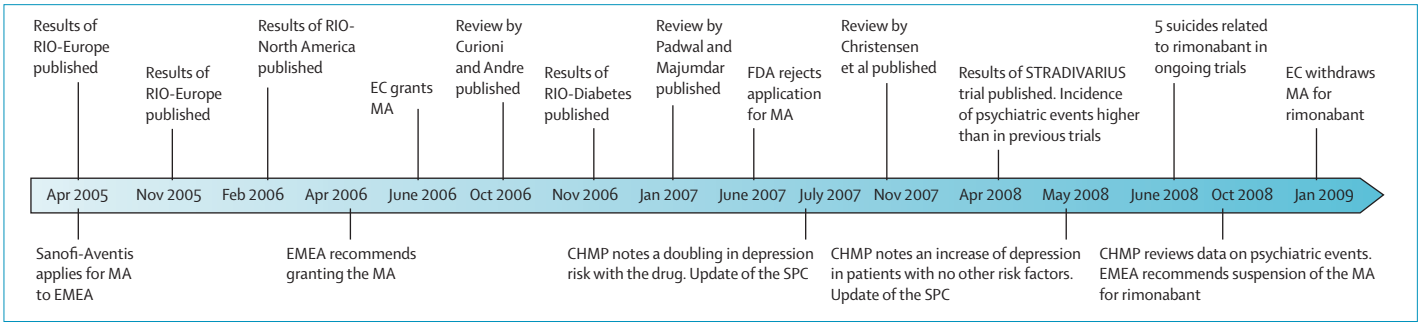

Figure: **Timeline of main procedural steps and available scientific information relative to rimonabant as a weight-loss drug**
CHMP=Committee for Medicinal Products for Human Use. EC=European Commission. EMEA=European Medicines Agency. FDA=Food and Drug Administration. MA=marketing authorisation. SPC=summary of product characteristics.

contrast with the absolute 10·9% difference in psychiatric disorders.[1]

We declare that we have no conflicts of interest.

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1 Topol EJ, Bousser M-G, Fox KAA, et al. Rimonabant for prevention of cardiovascular events (CRESCENDO): a randomised, multicentre, placebo-controlled trial. *Lancet* 2010; **376:** 517–23.
2 Christensen R, Kristensen PK, Bartels EM, Bliddal H, Astrup A. Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. *Lancet* 2007; **370:** 1706–13.
3 Curioni C, Andre C. Rimonabant for overweight or obesity. *Cochrane Database Syst Rev* 2006; **4:** CD006162.
4 FDA. Rimonabant briefing document. http://www.fda.gov/ohrms/dockets/AC/07/briefing/2007-4306b1-fda-backgrounder.pdf (accessed Sept 1, 2010).
5 EMEA. The European Medicines Agency recommends suspension of the marketing authorisation of Acomplia. London: European Medicines Agency, 2008. http://www.emea.europa.eu/humandocs/PDFs/EPAR/acomplia/53777708en.pdf (accessed Sept 1, 2010).

I was dismayed to read that the CRESCENDO trial of rimonabant to prevent cardiovascular events[1] was prematurely terminated. This is indeed a setback because obesity is a major health hazard, especially in the USA, and an effective anti-obesity drug is needed.

The question is why did rimonabant lead to a higher frequency of suicide? The answer to this question might be found in a study which noted that, in 262 cases of suicide, the frequency of *CYP2D6* gene duplication was ten-fold higher than in the general population.[2] Thus, patients with a duplication of the *CYP2D6* gene, which codes for a drug-metabolising enzyme also involved in the formation of serotonin, are more prone to suicide.

Additionally, why patients with depression were not excluded from the study, given the obvious connection between depression and suicide, is not clear. Indeed, depressed patients with a *CYP2D6* gene duplication might be further predisposed to suicide owing to the hypermetabolism of antidepressant medications in these patients.

Although the mechanism by which an extra copy of *CYP2D6* increases the risk of suicide remains to be determined, it is important to know whether duplication of *CYP2D6* was present in the patients in the CRESCENDO trial who committed suicide. Therefore, I suggest that this trial be reanalysed, excluding patients who had a duplication of the *CYP2D6* gene—assuming the DNA samples are available. If not, I suggest that another trial should be done that excludes patients with *CYPD26* duplications as well as those with depression.

I declare that I have no conflicts of interest.

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1 Topol EJ, Bousser M-G, Fox KAA, et al. Rimonabant for prevention of cardiovascular events (CRESCENDO): a randomised, multicentre, placebo-controlled trial. *Lancet* 2010; **376:** 517–23.
2 Zackrisson AL, Lindblom B, Ahlner J. High frequency of occurrence of *CYP2D6* gene duplication/multiduplication indicating ultrarapid metabolism among suicide cases. *Clin Pharmacol Ther* 2010; **88:** 354–59.

Authors' reply

We appreciate the perspective of Dominique Roberfroid and colleagues. However, our trial's premature discontinuation was not directly related to marketing of the drug. The regulatory authorities in several European countries requested cessation of enrolment into the trial, which led to its abrupt, unplanned termination. As stated in the paper,[1] our Data and Safety Monitoring Board had serially and carefully reviewed the neuropsychiatric side-effect data in the trial's participants and strongly advised continuation.

There were four suicides in the rimonabant group (0·07%) and one in the placebo group (0·02%). The number of deaths for bariatric surgery, a widely used alternative treatment for severe obesity, would have been expected to be far greater, and in centres of excellence has been reported to be 0·3% at 90 days.[2] Our hypothesis was that the low risk of suicide and serious neuropsychiatric effects would be counterbalanced by a significant reduction in cardiovascular death, heart attack, or stroke. Certainly such a trade-off would be