Response to letter from Löwe A. et al regarding article "Low-Density Lipoprotein Cholesterol Lowering for the Primary Prevention of Cardiovascular Disease Among Men With Primary Elevations of Low-Density Lipoprotein Cholesterol Levels of 190 mg/dL or Above: Analyses From the WOSCOPS (West of Scotland Coronary Prevention Study) 5-Year Randomized Trial and 20-Year Observational Follow-Up"

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To the editor,

We thank *Löwe et al* for their interest in our recent study[1] and the opportunity to offer further clarifications. Although we acknowledge the interest of the question raised by *Löwe et al*, we think they miss the main rationale and research question of our analysis,[1] namely to provide the only randomised controlled trial (RCT) evidence in primary prevention for lipid-lowering among individuals with low-density lipoprotein-cholesterol (LDL-C) >190 mg/dL, a level consistent with inherited or genetic dyslipidaemia (primary hypercholesterolaemia). Current guidelines cite that statins are likely to be beneficial for such patients, but also acknowledge that there are no direct

RCT evidence to support these recommendations. Given ethical concerns that would be posed by giving placebo to patients with LDL-C >190 mg/dL, the WOSCOPS data offers the only option to answer this question.[1] The authors cite that the unanswered question is "will providing statins to people at low risk of atherosclerosis cardiovascular disease (ASCVD) lower their risk even more?" This has been at least partly answered by the HOPE-3 trial[2] where the annual cardiovascular disease event rate was 0.7% per year in the placebo group and rosuvastatin reduced cardiovascular risk by about one quarter; however, the patients in that trial did not have elevated LDL-C as in WOSCOPS.

We disagree with comments regarding The Pooled Cohorts Equation (PCE), which we should point out has been validated and outperformed SCORE and other approaches in two European populations and performed at least as well as SCORE in the EPIC-NORFOLK study.[3-5] In addition, using the MESA cohort for the evaluation of the predictive utility of the PCE, as in the paper referenced by Löwe et al, has raised concerns as outlined by Goff et al.[6] Even with the high proportion of smokers in our analysis, this exposure was incorporated, and so accounted for, in the risk equation. If treatment decisions were made on the basis of a risk prediction tool rather than LDL-C levels, then statin therapy would have been withheld in about 67% of our cohort with LDL-C >190 mg/dL, in whom the 10-year predicted risk was <7.5%, in contrast to the actual observed risk of approximately 15%.[1] Individuals with primary severe hypercholesterolemia are likely to have an underlying genetic component to their LDL-C elevation and, therefore, an integrated lifetime exposure to high LDL-C that is not reflected in a risk score algorithm; this aligns with the concept of cumulative LDL-C exposure over time as a determinant of the progression and risk of ASCVD ("LDL-C

levels x years"),[7] which is inaccurately captured using a single LDL-C level measurement at one specific time-point. All this suggests that in cases of primary severe elevations of LDL-C conventional risk prediction tools may underestimate cardiovascular risk, and our findings suggest that risk prediction tools should not be routinely used when LDL-C is >190 mg/dL (primary elevations), as already stated in guidelines. Thus our findings strengthen current guideline recommendations. Statin therapy in the same population lowered the 10-year risk to <10%;[1] thus, among populations with primary LDL-C >190 mg/dL we believe that such individuals are at elevated lifetime risk and that early initiation of statins (small reductions maintained over time) would translate into meaningful benefits, as also suggested by our extended follow-up data.[1] While guidelines are recommendations and individual patients should be considered on an individual basis for prescription of therapy, including those with LDL-C >190 mg/dL, it must also be noted that using a risk scoring system to deny treatment to patients that may benefit of it would not be best practice. Our study provides a solid evidence-base for the clinician who decides on the basis of a full assessment including other risk factors, family history, querying familial hypercholesterolemia, or, in the future, a potential genetic score to decide on statin prescription.

Finally, as we already acknowledged in the Source of Funding section of our article,[1] the present analyses were partly funded by a grant from Sanofi to Imperial College London; this grant was for statistical analysis, which was performed, independently of sponsors, at Glasgow University where the WOSCOPS database is kept. For the avoidance of doubt, we provide assurance that the sponsors did not have any role nor influence the analysis presented in the article.

Disclosure statement

Dr Vallejo-Vaz reports honoraria for lecture from Amgen. Dr Packard reports grants and/or personal fees from MSD, Pfizer, Sanofi, and Roche, outside the submitted work. Dr Ray reports grants and/or personal fees from Pfizer, MSD, Astra Zeneca, Sanofi, Aegerion, Regeneron, Abbvie, Kowa, Cerenis, Medicines Company, Lilly, Esperion, Amgen, Cipla, and Algorithm, outside the submitted work.

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