Similar progression of diabetic retinopathy with insulin glargine and neutral protamine Hagedorn (NPH) insulin in patients with type 2 diabetes: a long-term, randomised, open-label study. Reply to Chantelau E [letter] and Currie CJ [letter]

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Abbreviations
DR Diabetic retinopathy
ETDRS Early Treatment Diabetic Retinopathy Study
NPH Neutral protamine Hagedorn
UKPDS UK Prospective Diabetes Study

To the Editor: We thank Dr E. Chantelau and Dr C. Currie for their interest [1, 2] in our findings [3], which we consider important because they are from a long-term randomised study that avoids the many limitations of retrospective database registry studies. They mainly commented on the power of the study and the possibility of performing post hoc sub-analyses. We would like to address their assertions, which we believe to be incorrect or misleading.

We strongly disagree with Dr Chantelau’s suggestion that the study was underpowered to detect changes in the rate of progression of diabetic retinopathy (DR) [1]. The sample size and power for the study were calculated based on these assumptions: a 20% 5 year background event rate; a non-inferiority margin of 10% (i.e. 50% of the background rate of 20%); approximately 60% of the randomised participants evaluable; and the two treatments being equivalent. Statistical power considerations are only rele-
vant during the study planning stage, to arrive at the sample size. On completion, the non-inferiority hypothesis will either be accepted or rejected, depending on the actual outcome observed, and the pre-study power assumption is no longer relevant. Nevertheless, had a 5 year background event rate of 15% been projected (our observed rates were 14.2% and 15.7% in the insulin glargine [A21Gly,B31Arg,B32Arg human insulin] and neutral protamine Hagedorn [NPH] insulin groups, respectively), with a non-inferiority margin of 7.5% (i.e. 50% of the background 15% rate) and a sample size that is the same as that of the per protocol population, the study would have had 81% power to demonstrate equivalence. Hence, the study was not underpowered.

Dr Chantelau also questioned the low frequency of DR at study entry (15.6% and 12.1% of patients reporting a medical history of DR in the insulin glargine and the NPH insulin groups, respectively; Table 1 of [3]), and objected to pooling patients with and without DR at baseline in assessing progression. Regarding the baseline prevalence of DR, Table 1 of our paper [3] also shows the frequency of DR based on grading of the baseline fundus photographs. By using this more sensitive measurement, a substantial proportion of patients were shown to have DR (~61% in both groups). Pooling patients with no DR and those with non-proliferative DR is appropriate when analysing, as we did, the prevalence of worsening by at least three steps on the Early Treatment Diabetic Retinopathy Study (ETDRS) retinopathy severity scale. To illustrate this, in the DCCT, this outcome was observed at 6 years in the primary prevention cohort (no DR) in 35% and 11% of the conventional and intensive treatment groups, respectively. The corresponding rates in the secondary prevention cohort (mild to moderate non-proliferative DR) were similar—31% and 11%, respectively [4]. In a subset of 1919 UK Prospective Diabetes Study (UKPDS) patients with appropriate photographs, the 6 year prevalence of worsening by three steps or more was 17.4% in 1216 patients without DR at baseline and 18.5% in 701 patients with non-proliferative DR [5].

Dr Currie [2] questions the selection of the patient population and the exclusion of established proliferative DR in the study, comments on the protective effects of metformin against cancer, proposes multiple arbitrary post hoc subgroup analyses, and notes that insulin glargine and NPH insulin resulted in similar glycaemic control. We believe that the population selected is indeed the population that should be studied, as it represents the majority of patients with type 2 diabetes treated with insulin who are seen in clinical practice. The entrance criteria allowed inclusion of a wide range of patients previously treated with human basal insulin, with or without regular insulin and oral agents; the resulting population closely matches that seen in clinical practice. The entry criteria did specify a particular range of DR, to assure a population in which assessment of the primary outcome would be most effective. The observed event rate for progression of three or more steps in ETDRS score in this study was ~15% at 5 years [3], and was similar to the rates in the UKPDS and DCCT [4, 5], as described above. Therefore, the suggestion that ‘… these patients could be those patients least likely to develop more severe visual loss …’ is incorrect.

Inclusion of patients with advanced forms of DR to assess progression, as Dr Currie suggested, is highly unreliable. In this study, no statistically significant difference in the development of proliferative DR was observed between the two groups, despite a greater frequency of the highest category of non-proliferative DR—in which progression of proliferative DR is most likely—at entry in the insulin glargine group.

The comparison of our randomised trial with a retrospective analysis on metformin and cancer is inappropriate. The percentage of patients using metformin was similar in both groups in this study (41% at baseline in the glargine group vs 42% with NPH, and 18% started after randomisation in the glargine group vs 16% with NPH) [3]; therefore, an imbalance of the effects of metformin could not have contributed to the findings. Furthermore, the publication authored by Currie et al. [6] and cited in his letter [2] actually demonstrated no increase in the frequency of cancer with insulin glargine compared with other insulins. There is no basis for Dr Currie’s speculative statement that ‘Akin to the safety issue with respect to cancer, it could be that insulin glargine does not trigger the [retinal] pathology, but, rather, promotes or accelerates the pathological process.’ Moreover, the question of the potential protective effects of metformin against cancer is difficult to evaluate in epidemiological analyses such as the ones Dr Currie cites, because of the tendency for metformin to be prescribed for younger and healthier patients. Regarding cancer risk with different insulins, our study is particularly relevant as it is the only randomised study to compare insulin glargine with human insulin, and because it shows no trend towards a greater risk of neoplasia with insulin glargine [7]. Recently published expert statements and objective criticisms have highlighted the possibilities for bias inherent in epidemiological, non-randomised comparisons of treatments [8–10].

The multiple subgroup analyses suggested by Dr Currie seem ill-advised for a randomised trial, in that (1) the diminished sample sizes of the subsets, with consequently much wider confidence intervals for statistical testing, weaken the conclusions that can be drawn; and (2) multiple post hoc analyses increase the chance of ‘uncovering’ findings that are statistically significant but spurious. Such post hoc sub-analyses can generate hypotheses, but neither provide final answers nor put to bed any lingering concerns.

Dr Currie notes that the slightly higher level of HbA1c observed with insulin glargine compared with NPH insulin...
was not emphasised in the paper. The study design clearly states the retinal primary objective and emphasises that testing differences in glycaemic control between the two insulins was not one of the study objectives. The intention was for glycaemic control to be as similar as possible in the two groups, despite insulin glargine being given once daily and NPH insulin twice daily, to avoid confounding the interpretation of the retinal outcomes. The requirement that NPH insulin be given twice daily vs once daily for insulin glargine actually provides a bias in favour of NPH insulin in titration of dosage. The small difference (0.2%) at study end in favour of NPH insulin is, therefore, not surprising. In any case, the upper bound of the two-sided 95% confidence interval for HbA1c treatment difference was 0.35%, which is within the non-inferiority margin of 0.4% conventionally accepted as a basis for clinical equivalence in efficacy of HbA1c between two treatments. This difference may be important mainly in strengthening the finding that retinopathy was not adversely affected by use of insulin glargine vs NPH insulin, despite slightly higher mean glucose. Finally, concerning hypoglycaemia, this study confirms findings from many other studies, which have consistently found a lower incidence of hypoglycaemia with insulin glargine treatment than with NPH insulin with otherwise similar regimens and at similar levels of glycaemic control [11–18].

In summary, we believe that the assertions made in these two letters are speculative and misguided. Our findings and conclusions are based on the largest and longest randomised trial comparing two types of insulin. The study design was appropriate to address concerns about the effects that insulin glargine might have on the progression of diabetic retinopathy, and the conclusions are well supported. We are confident that the reassuring findings and conclusions are correct as reported.

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