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LETTER TO THE EDITOR

WILEY

Comment on "a comparative effectiveness study of degludec and insulin glargine 300 U/mL in insulin-naïve patients with type 2 diabetes"

To the Editor:

Tibaldi et al. report results of the propensity-matched observational CONFIRM study[1] in previously insulin-naïve adults with type 2 diabetes, comparing two second-generation basal insulins. Using patients' electronic medical records from a large US database, they report an association between treatment with insulin degludec (IDeg) and a reduction in glycated haemoglobin (HbA1c) and hypoglycaemia rates, compared with insulin glargine 300 units/mL (Gla-300).

The results are in marked contrast to previously reported comparisons of these insulins[2–4] and a recent randomized controlled trial (RCT)[5] comparing the same basal insulins in broadly the same patient population, which found equivalent effects on both HbA1c and hypoglycaemia over a 6-month treatment period. Reasonably, we might have expected to see results that were similar at least on a ratio scale. Unfortunately, there are important flaws in the CONFIRM propensity score matching, which probably explain this discrepancy and confound any conclusions that may be drawn from the CONFIRM study.

The matching of cohorts in terms of hypoglycaemia prior to insulin initiation is clearly suboptimal (Supporting Information Table S2) and it is this imbalance at baseline, rather than the effects of treatment (as reported), that drives the differences in the final results. Helpfully, Tibaldi et al. have provided the data required to undertake conventional statistical testing of baseline differences, although these tests are not reported in the manuscript. For example, baseline hypoglycaemia rates (events per patient year exposed [PPYE]) for the matched population (IDeg 0.26 events/PPYE vs Gla-300 0.22 events/PPYE) were significantly different, with a P value of 0.007. Moreover, the population used in the hypoglycaemia analysis (a subgroup representing around two-thirds of the 4056 supposedly matched patients) had baseline differences that were even greater (IDeg 0.301 events/PPYE vs Gla-300 0.210 events/PPYE).

By presenting the results as a ratio of the pre- and post-treatment rates of hypoglycaemia, the authors effectively ignore the unmatched baseline values and obfuscate the fact that actual "on-treatment" outcomes were the same (IDeg 0.391 events/PPYE vs Gla-300 0.389 events/PPYE).

Other key patient characteristics differed between the "matched" groups at baseline, including body mass index (P = 0.01) and HbA1c (P = 0.008), and this raises particular concerns about the validity of any conclusions on the primary endpoint. Missing data and analyses conducted on a subset of the matched populations are a major challenge in CONFIRM. We invite the authors to provide baseline data on the subgroup of patients available for the HbA1c analysis to allow proper assessment of their findings.

It is completely plausible that these mismatches between the patient groups, rather than differences in the treatments received by the patients, explain the results presented and these imbalances can explain why the CONFIRM results differ from the RCT results.

Real-world studies, which provide data gathered from actual patient experiences and diverse patient populations, are valuable and encouraged.[6,7] However, while maximising external validity (generalisability), real-world studies will lack internal validity (unlike RCTs) if matching is not successful. Unfortunately, adequate matching is not achieved in the study by Tibaldi et al.

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CONFLICT OF INTEREST

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Peer Review

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