Letter to the Editor Concerning “Glycosylated Hemoglobin as a Surrogate for the Prediction of Cardiovascular Events in Cardiovascular Outcome Trials Comparing New Antidiabetic Drugs to Placebo”

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Dear Editor,

As an indicator of long-term glycemic control in patients with diabetes mellitus (DM), glycosylated hemoglobin (HbA_{1c}) has proved to be superior over fasting blood sugar as a reliable and a more accurate measure of diabetes treatment [1]. Although the clinical implications of HbA_{1c} have been highlighted by widely cited guidelines in relation to the microvascular complications of DM [2], the role of HbA_{1c} in predicting cardiovascular (CV) outcome is being cumulatively investigated [3].

An increasing body of knowledge supports the independent and linear association of HbA_{1c} level and the severity of atherosclerotic peripheral arterial disease (PAD) [4, 5], the literature has taken the prognostic value of HbA_{1c} to the next level, i.e., predicting the incidence of macrovascular diseases in nondiabetic individuals [3, 5, 6].

The timely publication of the paper by Ambrosi et al. [7] in a recent issue of *Cardiology* highlights a valuable standpoint for clinical trials of antidiabetic drugs to consider HbA_{1c} as a predictive measure for the CV benefits of the new medications being tested. As this meta-analysis concludes, mean decrease in HbA_{1c} is directly correlated with a reduction in major CV events. Furthermore,

such a relationship is independent of the weight loss observed during the study period of the included clinical trials. We sought to provide a few perspectives from which this research study could be interpreted more practically.

This meta-analysis could have drawn a clearer picture of the history of DM-related CV complications at the baseline for each of the included clinical trials. While there might have been a lack of information at the individual level, the frequency of CV disease of any type at the time of enrollment has been depicted for each trial and it ranged from 41 to 100% of the patients. If provided, the relationship between post-treatment HbA_{1c} alteration and the de novo incidence of CV complications of DM would be much clearer.

Although the change in HbA_{1c} was correlated with the change in CV events at the end of the follow-up period, the duration of follow-up was not highlighted in the meta-analysis. Previous studies have shown the clinical utility of HbA_{1c} as a predictor of short-term mortality after acute coronary syndrome, and it also bears prognostic value for long-term CV complications of lesser severity. In either case, more elaboration on the follow-up period

during which the incidence of CV events was measured against the net change in HbA_{1c} would have expanded our concept of its time-sensitive predictive value.

Interestingly, the relative change in the major CV events between the new antidiabetic drug and placebo ranged from -3 to 26% compared to the unidirectional change in HbA_{1c} percentage. A sensitivity analysis excluding these outliers would shed a brighter light on the relationship between HbA_{1c} and CV events.

The meta-analysis by Ambrosi et al. [7] truly highlights the easing role of a universally accepted marker as a surrogate for the prediction of CV outcomes in clinical trials of antidiabetic drugs. However, the above-men-

tioned points can widen our perspectives from which this clinical surrogate is viewed by investigators of future research studies.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

All authors contributed to the conception of this manuscript, its preparation, and intellectual approval of the final draft.

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