Authors' Reply to the Letter by Shoar et al. on "Glycosylated Hemoglobin as a Surrogate for the Prevention of Cardiovascular Events in Cardiovascular Outcome Trials Comparing New Antidiabetic Drugs to Placebo"

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Dear Editor,

According to the suggestion by Shoar et al. [1], we tested the robustness of the correlation between HbA1c reduction and MACE decrease, performing sensitivity analyses [2].

The predictive value of HbA1c for coronary events has been consistently shown in the early period following an acute coronary event [3]. There is also some evidence that HbA1c predicts survival in diabetic patients with stable coronary artery disease [4]. In our meta-analysis, 2 trials included patients with a recent acute coronary syndrome and 12 trials included patients either at high risk or with definite coronary artery disease (stable or unstable). Excluding the 2 trials performed after an acute

coronary syndrome did not modify the correlation ($R = 0.88$, $p = 0.0004$).

In the 5 trials testing a DPP-4 inhibitor, the relative MACE reduction was at most 3%, despite a significant (modest) reduction in HbA1c. Excluding these 5 trials did not modify the correlation between HbA1c reduction and MACE decrease ($R = 0.84$, $p = 0.004$).

Lastly, we excluded the SUSTAIN-6 trial showing the higher MACE decrease (26%). The correlation was not significantly modified ($R = 0.88$, $p < 0.001$).

Thus, we are confident that HbA1c reduction explains, at least in part, the decrease in MACE observed with the new antidiabetic drugs.

References

- 1 Shoar S, Naderan M, Shoar N, Modukuru VR. 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". *Cardiology*. 2020.
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- 3 Pan W, Lu H, Lian B, Liao P, Guo L, Zhang M. Prognostic value of HbA1c for in-hospital and short-term mortality in patients with acute coronary syndrome: a systematic review and meta-analysis. *Cardiovasc Diabetol*. 2019 Dec;18(1):169.
- 4 Mancini GB, Maron DJ, Hartigan PM, Spertus JA, Kostuk WJ, Berman DS, et al.; COURAGE Trial Research Group. Lifestyle, glycosylated hemoglobin A1c, and survival among patients with stable ischemic heart disease and diabetes. *J Am Coll Cardiol*. 2019 Apr;73(16):2049–58.