COMMENT ON LAITEERAPONG ET AL.

The Legacy Effect in Type 2 Diabetes: Impact of Early Glycemic Control on Future Complications (The Diabetes & Aging Study). Diabetes Care 2019;42: 416–426

Adam Hulman,[1,2] Lasse Bjerg,[1,2,3] and Bendix Carstensen[3]

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We read with interest the article from Laiteerapong et al. (1) about the effect of early glycemic control on micro- and macrovascular complications and mortality in individuals with newly diagnosed type 2 diabetes. However, we have major concerns regarding their study.

First, we are concerned about the use of conditioning on the future when selecting the study sample, i.e., those still alive 10 years after diagnosis, while including this period in the follow-up time. The authors cautiously mentioned this as a limitation (lack of generalizability); however, we think that conditioning on the future makes the mortality figures erroneous and the interpretation of the complication results problematic with substantially limited clinical utility. The authors fitted a total number of seven Cox regression models for each outcome, with increasing duration of exposure (from 0–1 to 0–7 years), to investigate whether the legacy effect depends on the exposure period. They report an increasing effect size with longer exposure to HbA_{1c} ≥8% (64 mmol/mol) on microvascular complications and mortality. As the sequence of models includes successively shorter time spans where deaths and follow-up prior to death have been removed, it is not surprising to see increasing effects on complications of variables that are known to influence mortality—the earliest follow-up will be most biased to the null. Furthermore, the authors analyzed each individual up to seven times using duplication of data. The same person enters in models with different baseline hazards for the same outcome. Comparison of hazard ratios from such models based on overlapping samples lacks quantified evidence from formal statistical testing, which calls for caution when drawing conclusions.

We also think that the mean HbA_{1c} is too crude to capture differences between different exposure periods. Not only is it susceptible to outliers, but also periods with more frequent measurements (which might not be random) can dominate its value. Unfortunately, it is difficult to assess the magnitude of this problem, as the authors have not reported information on the timing and frequency of the HbA_{1c} measurements.

To avoid conditioning on the future and duplication of data, inclusion of all follow-up data and an alternative modeling strategy are recommended. The Poisson model framework with split follow-up time makes it possible to include time-updated exposures and handle multiple timescales (2). Instead of using a categorized exposure variable, nonlinear interactions between time-updated HbA_{1c} and time since diagnosis could be explored by including natural cubic spline terms. This would give estimates of the HbA_{1c} effect for different times since diagnosis. The legacy effect would be addressed by including the extra cumulative mean effect of HbA_{1c} at a fixed time relative to the time-updated HbA_{1c} effect. The association between HbA_{1c} and the outcomes could be presented at different times since diagnosis. Furthermore, multiple complications can be handled in this framework simultaneously, as demonstrated in our recent article (3). Alternatively, the joint modeling framework could be considered, as it allows more complex association structures, such as the weighted cumulative effect of an exposure, to be explored (4).

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[1]*Aarhus University, Aarhus, Denmark*
[2]*Danish Diabetes Academy, Odense, Denmark*
[3]*Steno Diabetes Center Copenhagen, Copenhagen, Denmark*

Corresponding author: Adam Hulman, adam.hulman@ph.au.dk