RESPONSE TO COMMENT ON LEWIS ET AL.

Management of Hemoglobin Variants Detected Incidentally in HbA_{1c} Testing: A Common Problem Currently Lacking a Standard Approach. Diabetes Care 2017;40:e8–e9

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We thank Drs. Little and Rohlfing for their comments (1) regarding our article on the management of incidental detection of hemoglobin (Hb) variants in HbA_{1c} testing (2). We agree that awareness of the potential for interference to affect HbA_{1c} results is essential in research and clinical care. Multiple studies (including that of Lin et al. [3]) prior to the 2016 article by Rohlfing et al. (4) had yielded no evidence of clinically significant bias resulting from HbAS or HbAC variants in Tosoh G8 results. In the Vitamin D and Type 2 Diabetes (D2d) Study, we excluded potential participants with HbAE and HbAD because clinically significant bias had been demonstrated.

In a recent article by Rohlfing et al. (4), HbA_{1c} testing using a Tosoh G8 with software version 5.20 was found to show clinically significant interference (5) in the presence of HbAS and HbAC at the 9% HbA_{1c} level (mean difference with comparative method, 0.76 percentage points for HbAC, 0.79 percentage points for HbAS). Interference at the 6% HbA_{1c} level, which is relevant to D2d given the study's focus on prediabetes, was not found to be clinically significant (0.33 percentage points for HbAC, 0.18 percentage points for HbAS). We acknowledge that "not clinically significant" is not equivalent to "no interference." Nonetheless, any potential interference should not have a meaningful effect on the conduct of the D2d Study because only 37 out of 2,423 participants have HbAS ($n = 27$) or HbAC ($n = 10$) variants, and HbA_{1c} is only one of three criteria used to define prediabetes or diabetes. Moreover, owing to the randomized design, the internal validity of D2d should not be affected.

Changes in assay properties are to be expected over the course of a long-term clinical trial such as D2d, and there have so far been two software updates to the Tosoh G8 used in the D2d central laboratory. The software version (5.20) noted in the article by Rohlfing et al. (4) was in use from June 2014 through December 2015, during which time only eight participants with HbAS or HbAC were randomized. Prior to that period, version 5.10 was used; version 5.23 has been in use since December 2015 and remains in place as we follow our study population. Review of older articles cited on the NGSP interferences web page (6) does not reveal which software versions may have been in use in those studies, and we are unaware of data on possible interferences rising to a level of clinical significance for versions 5.10 and 5.23. To our knowledge, version 5.24 is not yet available in the U.S.

When selecting an HbA_{1c} assay for research, avoiding interference due to rare Hb traits is important and needs to be balanced with other factors. The low coefficient of variation of the ion exchange high-performance liquid chromatography method we chose is desirable for a study such as D2d because it optimizes internal validity.

We agree with Little and Rohlfing (1) that the HbA_{1c} assay is not as straightforward as is sometimes thought and that more work is needed both to understand operational characteristics (especially in individuals with Hb variants) and to define its role as a diagnostic criterion for diabetes. D2d is the first large trial to use HbA_{1c} as one of the inclusion criteria for prediabetes and as a diagnostic criterion for diabetes; therefore, it represents an ideal setting in which to gain insight into these complex issues.

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