



COMMENT ON DAVIS ET AL.

Effects of Severe Hypoglycemia on Cardiovascular Outcomes and Death in the Veterans Affairs Diabetes Trial. *Diabetes Care* 2019;42:157–163

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The recent article by Davis et al. (1) reports on the relationship between severe hypoglycemic events (SHEs) and the subsequent risk of cardiovascular (CV) events or death observed in the Veterans Affairs Diabetes Trial (VADT). Unfortunately, the authors did not acknowledge our article published earlier this year in *Diabetes Care*, “Increased Risk of Severe Hypoglycemic Events Before and After Cardiovascular Outcomes in TECOS Suggests an At-Risk Type 2 Diabetes Frail Patient Phenotype” (2). Accordingly, they missed an opportunity to potentially confirm the intriguing reverse scenario we identified, i.e., a relationship between nonfatal CV events and the subsequent risk of SHEs. Given that there appear to be common traits for patients suffering SHEs and/or CV events or death, it would clearly be of interest to explore the situation in VADT. Furthermore, the hazard ratios given in Table 3 of the article by Davis et al., suggesting increased risks of CV events and death subsequent to SHEs within the prior 3 months, do not appear to be adjusted fully for potential confounders. Their Table 2 shows that, for example, autonomic neuropathy and proteinuria were significant predictors of SHEs in VADT.

However, these characteristics were not included in the adjustment of the hazard ratios listed in Table 3, despite these findings and the widespread recognition that these variables are also strong predictors of CV events and death. It would be helpful to know whether the Table 3 hazard ratios remain significant after complete adjustment for all characteristics found to be associated with increased risk of SHEs. It would also be of interest to provide the difference in absolute numbers between the two randomized treatment arms in VADT for CV events and deaths in the first 3 months after an SHE, to better understand the potential worst-case scenario for the overall “contribution” of SHEs to the VADT primary outcome (3).

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References

1. Davis SN, Duckworth W, Emanuele N, et al.; Investigators of the Veterans Affairs Diabetes Trial. Effects of severe hypoglycemia on cardiovascular outcomes and death in the Veterans Affairs Diabetes Trial. *Diabetes Care* 2019;42:157–163
2. Standl E, Stevens SR, Armstrong PW, et al.; TECOS Study Group. Increased risk of severe hypoglycemic events before and after cardiovascular outcomes in TECOS suggests an at-risk type 2 diabetes frail patient phenotype. *Diabetes Care* 2018;41:596–603
3. Duckworth W, Abraira C, Moritz T, et al.; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes [published correction appears in *N Engl J Med* 2009; 361:1028]. *N Engl J Med* 2009;360:129–139

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The authors of the cited article did not respond.

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