

Severe Hypoglycemia and Cardiovascular Disease in Type 2 Diabetes

Hyeong Kyu Park

Department of Internal Medicine, Soonchunhyang University College of Medicine, Seoul, Korea

Cardiovascular disease (CVD) is the main cause of morbidity and mortality in subjects with diabetes mellitus (DM). Strict glycemic control has been shown to reduce the risk of microvascular complications of DM, but its effects on the risk of CVD appear less conclusive. Recent large randomized trials have demonstrated that intensive glycemic control failed to show significant benefits on the macrovascular outcomes. In particular, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study has shown that participants in intensive therapy had 22% higher mortality with 3-fold higher incidence of severe hypoglycemia than those in standard therapy, suggesting a possible association between hypoglycemia and increased mortality [1]. However, the *post hoc* analysis of ACCORD study suggested that the high mortality in the intensive treatment group was not directly explained by higher rate of hypoglycemia [2]. In contrast, a retrospective analysis of the Action in Diabetes and Vascular Disease: Preterax and Diamiron Modified Release Controlled Evaluation (ADVANCE) study has shown that severe hypoglycemia is strongly associated with an increased risk of macrovascular events, presenting hypoglycemia as a possible cause for adverse cardiovascular events and deaths [3]. Furthermore, several epidemiologic studies have demonstrated that symptomatic or severe hypoglycemia is associated with an increased risk of cardiovascular events and mortality in patients with type 2 diabetes mellitus (T2DM) [4,5].

Hypoglycemia occurs commonly during the treatment of DM and is also a major hurdle to attaining better glycemic con-

trol. Experience of hypoglycemic episodes can discourage subjects with DM from achieving their glycemic goals, breaking patient's will to keep optimal glycemic control. Among the categories of hypoglycemia, severe hypoglycemia is generally defined as an event that requires the assistance of another person to overcome hypoglycemia, posing a serious health problem in subjects with DM [6]. As discussed earlier, hypoglycemia appears to be associated with adverse cardiovascular events and deaths in large clinical trials and several epidemiologic studies, even though no direct evidence of causal relationship between hypoglycemia and increased cardiovascular mortality has been found in patients with DM until now. There are potential mechanisms by which acute hypoglycemia may increase cardiovascular events and deaths. Acute hypoglycemia induces sympathoadrenal activation, endothelial dysfunction, vasoconstriction, prolongation of QT interval, enhanced inflammation, and increased thrombogenesis [7-9]. All of these physiological changes may trigger myocardial ischemia and cardiac arrhythmia in patients with DM, which could cause adverse cardiovascular events and deaths (Fig. 1).

The major causes of hypoglycemic episodes in patients with T2DM are changes related to diet, exercise, or glucose-lowering medications. In addition, clinical factors that predispose to hypoglycemia include advanced age, polypharmacy, low education level, poor cognitive function, intensive glycemic control, longer duration of DM, and longer duration of insulin therapy. Peripheral or autonomic neuropathy is also associated with hypoglycemia [10]. In particular, hypoglycemia unawareness or a

Corresponding author: Hyeong Kyu Park
Department of Internal Medicine, Soonchunhyang University Hospital,
Soonchunhyang University College of Medicine, 59 Daesagwan-ro,
Yongsan-gu, Seoul 04401, Korea
E-mail: hkpark@schmc.ac.kr

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

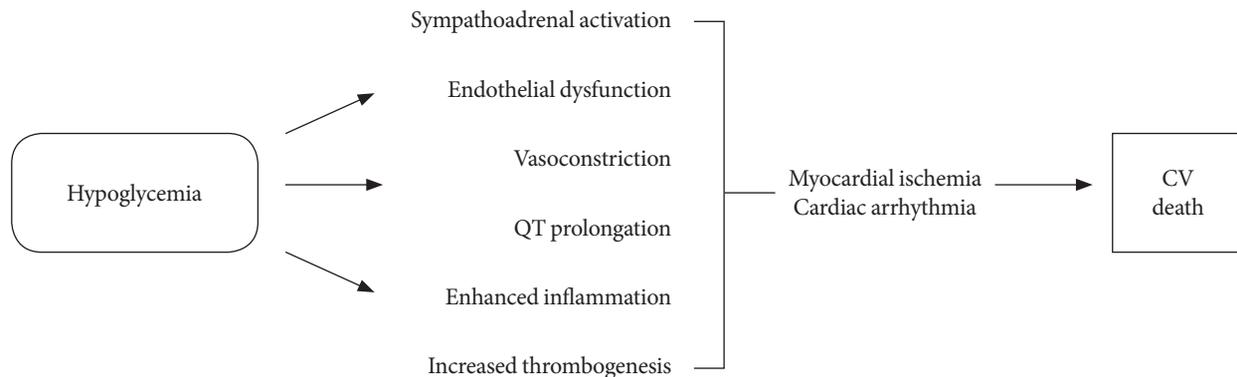


Fig. 1. Potential mechanisms linking hypoglycemia with adverse cardiovascular events and death. CV, cardiovascular.

history of previous hypoglycemia may increase the risk of severe hypoglycemia. Albuminuria or impaired renal function is associated with hypoglycemia in patients with DM [11,12].

In this issue, Yun et al. [13] presented an article showing that a history of CVD might be an independent risk factor for the development of severe hypoglycemia in Korean patients with T2DM. They enrolled 894 patients with T2DM aged 25 to 75 years without chronic kidney disease and conducted a prospective cohort study. A total of 624 patients completed the follow-up with a median time of 9.5 years (5,814 person-years). They showed that the development of severe hypoglycemia was associated with a history of CVD after adjustment for age, sex, duration of T2DM, diabetic complications, insulin use, and glycosylated hemoglobin level. In a previous study from the same cohort, they demonstrated that the presence of definite cardiovascular autonomic neuropathy (CAN) was a prognostic factor for the development of severe hypoglycemia [10]. They found in this study that even after adjusting further for the presence of CAN, patients with a history of CVD had nearly 2-fold higher risk of future development of severe hypoglycemia compared with those without.

In accordance with these findings, several case-control or population-based studies in patients with T2DM have demonstrated that the presence of coronary heart disease or stroke might be an independent risk factor for severe hypoglycemia [14-16]. Moreover, a retrospective study in T2DM patients who were admitted for severe hypoglycemia has shown that patients with a history of coronary artery disease (CAD) are at an increased risk for recurrent hypoglycemia during the first 48 hours after admission compared with those without [17]. On the contrary, several conflicting data suggested that a history of prior CVD did not predict hypoglycemia in patients

with DM [18-20]. Therefore, further studies in other races or ethnic groups will be necessary to confirm these findings.

As the authors noted, there are several limitations in this study. First, though the follow-up time is quite long, the size of study patients is relatively small. Second, the definition of CVD is narrow, which includes CAD and stroke but excludes peripheral artery disease. Moreover, plausible mechanisms relating a history of CVD to an elevated risk of severe hypoglycemia remain thus far speculative. Despite some limitations, the current study provides valuable information suggesting that a history of prior CVD is an independent risk factor for the future development of severe hypoglycemia in patients with T2DM, prompting practitioners to address this possibility in vulnerable patients. In addition, studies to explore the underlying mechanisms linking CVD with severe hypoglycemia are needed.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Action to Control Cardiovascular Risk in Diabetes Study Group, Gerstein HC, Miller ME, Byington RP, Goff DC Jr, Bigger JT, Buse JB, Cushman WC, Genuth S, Ismail-Beigi F, Grimm RH Jr, Probstfield JL, Simons-Morton DG, Friedewald WT. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358:2545-59.
2. Bonds DE, Miller ME, Bergenstal RM, Buse JB, Byington RP, Cutler JA, Dudl RJ, Ismail-Beigi F, Kimel AR, Hoogwerf B,

- Horowitz KR, Savage PJ, Seaquist ER, Simmons DL, Sivitz WI, Speril-Hillen JM, Sweeney ME. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. *BMJ* 2010;340:b4909.
3. Zoungas S, Patel A, Chalmers J, de Galan BE, Li Q, Billot L, Woodward M, Ninomiya T, Neal B, MacMahon S, Grobbee DE, Kengne AP, Marre M, Heller S; ADVANCE Collaborative Group. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med* 2010;363:1410-8.
 4. Moheet A, Seaquist ER. Hypoglycemia as a driver of cardiovascular risk in diabetes. *Curr Atheroscler Rep* 2013;15:351.
 5. Goto A, Arah OA, Goto M, Terauchi Y, Noda M. Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis. *BMJ* 2013;347:f4533.
 6. Yun JS, Ko SH. Avoiding or coping with severe hypoglycemia in patients with type 2 diabetes. *Korean J Intern Med* 2015;30:6-16.
 7. Morales J, Schneider D. Hypoglycemia. *Am J Med* 2014;127(10 Suppl):S17-24.
 8. Frier BM. Hypoglycaemia in diabetes mellitus: epidemiology and clinical implications. *Nat Rev Endocrinol* 2014;10:711-22.
 9. Rana OA, Byrne CD, Greaves K. Intensive glucose control and hypoglycaemia: a new cardiovascular risk factor? *Heart* 2014;100:21-7.
 10. Yun JS, Kim JH, Song KH, Ahn YB, Yoon KH, Yoo KD, Park YM, Ko SH. Cardiovascular autonomic dysfunction predicts severe hypoglycemia in patients with type 2 diabetes: a 10-year follow-up study. *Diabetes Care* 2014;37:235-41.
 11. Amiel SA, Dixon T, Mann R, Jameson K. Hypoglycaemia in type 2 diabetes. *Diabet Med* 2008;25:245-54.
 12. Yanai H, Adachi H, Katsuyama H, Moriyama S, Hamasaki H, Sako A. Causative anti-diabetic drugs and the underlying clinical factors for hypoglycemia in patients with diabetes. *World J Diabetes* 2015;6:30-6.
 13. Yun JS, Ko SH, Ko SH, Song KH, Yoo KD, Yoon KH, Park YM, Ahn YB. Cardiovascular disease predicts severe hypoglycemia in patients with type 2 diabetes. *Diabetes Metab J* 2015;39:498-506.
 14. Holstein A, Hahn M, Patzer O, Seeringer A, Kovacs P, Stingl J. Impact of clinical factors and CYP2C9 variants for the risk of severe sulfonylurea-induced hypoglycemia. *Eur J Clin Pharmacol* 2011;67:471-6.
 15. Quilliam BJ, Simeone JC, Ozbay AB. Risk factors for hypoglycemia-related hospitalization in patients with type 2 diabetes: a nested case-control study. *Clin Ther* 2011;33:1781-91.
 16. Hsu PF, Sung SH, Cheng HM, Yeh JS, Liu WL, Chan WL, Chen CH, Chou P, Chuang SY. Association of clinical symptomatic hypoglycemia with cardiovascular events and total mortality in type 2 diabetes: a nationwide population-based study. *Diabetes Care* 2013;36:894-900.
 17. Lin YY, Hsu CW, Sheu WH, Chu SJ, Wu CP, Tsai SH. Risk factors for recurrent hypoglycemia in hospitalized diabetic patients admitted for severe hypoglycemia. *Yonsei Med J* 2010;51:367-74.
 18. Davis TM, Brown SG, Jacobs IG, Bulsara M, Bruce DG, Davis WA. Determinants of severe hypoglycemia complicating type 2 diabetes: the Fremantle diabetes study. *J Clin Endocrinol Metab* 2010;95:2240-7.
 19. Tschöpe D, Bramlage P, Binz C, Krekler M, Deeg E, Gitt AK. Incidence and predictors of hypoglycaemia in type 2 diabetes: an analysis of the prospective DiaRegis registry. *BMC Endocr Disord* 2012;12:23.
 20. Kong AP, Yang X, Luk A, Ma RC, So WY, Ozaki R, Ting R, Cheung K, Ho CS, Chan MH, Chow CC, Chan JC. Severe hypoglycemia identifies vulnerable patients with type 2 diabetes at risk for premature death and all-site cancer: the Hong Kong diabetes registry. *Diabetes Care* 2014;37:1024-31.