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Difference In Non-Severe Hlypolgycemia Risk For Sodium And Sulfonylurea- Randomized Controlled Trial Using Glucose Contransporter-2 Inhibitors (SGLT2-I) As An Add-On To Metforrmin

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Abstract

Background: Non-severe hypoglycemia impairs quality of life, productivity, and well-being while also raising treatment expenses. The non-severe hypoglycemia rate associated with the use of sulfonylureas (SU) in comparison to newer classes like SGLT2-I may be clinically significant.

Objective: To investigate the non-severe hypoglycemia risk difference (RD) between SU usage and SGLT2-I in randomised controlled trials (RCTs) as a supplement to metformin.

Methods: A search for RCTs of SGLT2-I was done. This search made use of the PubMed database. The search was restricted to RCTs for canagliflozin, dapagliflozin, and empagliflozin that were published in the English language. SU The dose of SUs was converted to glimepiride equivalent doses using dose comparison.

Conclusion: This study showed that a significant number of individuals who were exposed to SU in SGLT2-I RCTs exhibited non-severe hypoglycemia compared to SGLT2-I. The likelihood of non-severe hypoglycemia episodes was significantly correlated with SU dosage.

Background:

Sulfonylureas (SUs) are known for their demonstrated effectiveness in decreasing blood sugar levels, low cost, and extensive clinical experience in the treatment of diabetes. 1 However, using SU carries a risk for hypoglycemia, both severe and mild. 1 Both severe and non-severe hypoglycemia are linked to a decreased quality of life in terms of health and an increase in the burden of disease. 2–5 Non-severe hypoglycemia decreases quality of life and well-being by raising anxiety and dread of recurring occurrences, which can have a detrimental impact on lifestyle choices, driving safety, and work productivity. 6,7 Severe hypoglycemia is typically characterised as a low blood sugar episode where the patient needs help from another person to actively administer carbs, glucagon, or conduct other remedial activities; if not, the episode can be classified as non-severe.

There are currently more than ten different kinds of drugs that can be used to treat diabetes. From the perspective of efficacy and safety profiles, each type of drug has its own benefits and drawbacks. 8,10. 8,10 Improved, patient-centered medication for diabetes is now more feasible than ever previously in this environment. 9 The risk of hypoglycemia may be decreased by newer groups of drugs such SGLT2-I, dipeptidyl peptidase 4 (DPP-4) inhibitors, and glucagon-like peptide 1 (GLP-1) receptor agonists. Clinical importance may be seen in the non-severe hypoglycemia rate attributable to SU use when compared to newer classes like SGLT2-I. This investigation's goal was to find out how frequently non-severe hypoglycemia caused by SU use in SGLT2-I RCTs.

Methods: We looked for randomised controlled trials (RCTs) of SGLT2-I in the PubMed database. Prior to January 15, 2016, published studies were included in the search. The search was restricted to RCTs for "canagliflozin," "dapagliflozin," and "empagliflozin" that were published in the English language. RCTs with at least one arm comparing SU to SGLT2-I in addition to metformin were chosen. The rate of non-severe hypoglycemia, study length, type, and dose (average mg/day) of SU and SGLT2-I were taken out of studies that satisfied the inclusion criteria. Further information was sought as needed by searching the ClinicalTrials.gov registry.

Both the SU arm and the SGLT2-I arm had non-severe hypoglycemia rates at 52 and 104 weeks. It should be noted that insulin was not utilised or reported for any of the RCTs' arms. Although there were some slight variations in how hypoglycemia episodes were defined throughout the selected RCTs (Appendix 1), they were highly comparable in how they distinguished between severe and non-severe hypoglycemia. Each one of them adhered to and integrated the standard definition of severe hypoglycemia, which is defined as an episode of low blood glucose requiring the aid of another person. For non-severe hypoglycemia rates, the risk difference (RD) between the SU arm and the SGLT2-I arm was computed. The Chi-square test was used to draw conclusions on the prevalence of non-severe hypoglycemia.

SU dosage as glimepiride equivalent doses (mg daily) were correlated with non-severe hypoglycemia rates using Pearson's correlation. Modeling non-severe hypoglycemia rates using average daily dosages of glimepiride for 52 and 104 weeks. Utilizing the data analysis programme Minitab 17, all data were re-reported as mean (SD).

REFERENCE:

1. Inzucchi SE, Bergenstal RM, Buse JB et al. Management of hyperglycemia in type 2 diabetes: a patient-centred approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabet Care 2012;35:1364–79.

2. Kalra S, Mukherjee JJ, Venkataraman S et al. Hypogly-cemia: The neglected complication. Indian J Endocrinol Metab 2013;17:819–34.

3. Williams SA, Shi L, Brenneman SK, Johnson JC, Wegner JC, Fonseca V. The burden of hypoglycemia on healthcare utilization, costs, and quality of life among type 2 diabetes mellitus patients. J Diabetes Complicat 2012;26:399–406.

4. Fidler C, Elmelund CT, Gillard S. Hypoglycemia: an overview of fear of hypoglycemia, quality-of-life, and impact on costs. J Med Econ 2011;14:646–55.

5. Harris S, Mamdani M, Galbo-Jorgensen CB, Bogelund M, Gundgaard J, Groleau D. The effect of hypoglycemia on health-related quality of life: Canadian results from a multinational time trade-off survey. Can J Diabetes 2014;38:45–52.

6. Brod M, Wolden M, Christensen T, Bushnell DM. A 9 country study of the burden of non-severe nocturnal hypoglycemic events on diabetes management and daily function. Diabetes Obes Metab 2013;15:546–57.

7. Brod M, Pohlman B, Wolden M, Christensen T. Non-severe nocturnal hypoglycemic events: experience and impacts on patient functioning and well-being. Qual Life Res 2013;22:997–1004.

8. Canadian Diabetes Association. Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2013 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada. Can J Diabetes 2013;37:S1–S212.

9. Inzucchi SE, Bergenstal RM, Buse JB et al. Management of hyperglycaemia in type 2 diabetes, 2015: a patient-centred approach. Update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetologia 2015;58:429–42.

10. No authors listed. Standards of medical care in diabe-tes--2015: summary of revisions. Diabetes Care 2015;38 Suppl:S4.

11. Pharmacist's Letter. Sulfonylurea dose comparison. Pharmacist's Letter/Prescriber's Letter 2009;25(8):250801 2009.

12. Nauck MA, Del PS, Meier JJ et al. Dapagliflozin ver-sus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin: a randomized, 52-week, double-blind, active-controlled noninferiority trial. Diabetes Care 2011;34:2015–2022.

13. Nauck MA, Del PS, Duran-Garcia S et al. Du-rability of glycaemic efficacy over 2 years with dapagliflozin versus glipizide as add-on therapies in patients whose type 2 diabetes mellitus is inadequately controlled with metformin. Diabetes Obes Metab 2014;16:1111–20.

14. Cefalu WT, Leiter LA, Yoon KH et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. Lancet 2013;382:941–50.

15. Leiter LA, Yoon KH, Arias P et al. Canagliflozin provides durable glycemic improvements and body weight reduc-tion over 104 weeks versus glimepiride in patients with type 2 diabetes on metformin: a randomized, double-blind, phase 3 study. Diabetes Care 2015;38:355–64.

16. Efficacy and Safety of Empagliflozin (BI 10773) With Metformin in Patients With Type 2 Diabetes. https://clinicaltrials /ct2/ show/study/NCT01167881?term5NCT01167881&rank51 2016.

17. Ridderstrale M, Andersen KR, Zeller C, et al. Com-parison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. Lancet Diabetes Endocrinol 2014;2:691–700.JPTCP_24_2_2017_Farahani_3_edited.indd 75/23/2017 4:21:22 PM

18. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047-1053.

19. Canadian Diabetes Association. An economic tsunami: the cost of diabetes in Canada. http://www diabetes ca/economic report/ [serial online] 2009.

20. Canadian Diabetes Association. The prevalence and costs of diabetes. Available at: http://www diabetes ca/diabetes-and-you/ what/prevalence/ [serial online] 2013.

21. Public Health Agency of Canada. Diabetes in Canada: Facts and figures from a public health perspective. Ottawa. Available at: http://www phac-aspc gc ca/cd-mc/publications/diabetes-diabete/facts-figures-faits-chiffres-2011/ [serial online] 2011.

22. Abdelhafiz AH, Rodriguez-Manas L, Morley JE, Sinclair AJ.

Hypoglycemia in older people - a less well recog-nized risk factor for frailty. Aging Dis 2015;6:156–67.

23. Farahani P, Khan S, Oatway M, Dziarmaga A. Explor-ing the distribution of prescription for sulfonylureas in patients with type 2 diabetes according to ardiovascular risk factors within a Canadian primary care setting. J Popul Ther Clin Pharmacol 2015;22:e228–e236.

24. Greiver M, Williamson T, Barber D et al. Prevalence and epidemiology of diabetes in Canadian primary care practices: a report from the Canadian Primary Care Sentinel Surveillance Network. Can J Diabetes 2014;38:179–85.

25. Ostenson CG, Geelhoed-Duijvestijn P, Lahtela J, et al. Self-reported non-severe hypoglycaemic events in Europe. Diabet Med 2014;31:92–101.

26. Geelhoed-Duijvestijn PH, Pedersen-Bjergaard U, Weit-gasser R, et al. Effects of patient-reported non-severe hypoglycemia on healthcare resource use, work time loss, and wellbeing in insulin-treated patients with diabetes in 7 European countries. J Med Econ 2013;16:1453–61.

27. Brod M, Christensen T, Thomsen TL, Bushnell DM. The impact of non-severe hypoglycemic events on work productivity and diabetes management. Value Health 2011;14:665–71.

28. Jensen MM, Pedersen-Bjergaard U. Self-reported fre-quency and impact of non-severe hypoglycemic events in insulin-treated diabetic patients in Denmark. Diabetes Management 2015;5:67–78.

29. 29.Kulzer B, Seitz L, Kern W. Real-world patient-reported rates of non-severe hypoglycaemic events in Germany. Exp Clin Endocrinol Diabetes 2014;122:167–72.

30. Weitgasser R, Lopes S. Self-reported frequency and impact of hypoglycaemic events in insulin-treated diabetic patients in Austria. Wien Klin Wochenschr 2015;127:36–44.

31. Canadian Agency for Drugs and Technologies in Health. Optimal Second- and Third-Line Therapy in Type 2 Diabetes. CADTH Report/Project in Briefs [Internet] Ottawa, ON: Author; 2011-2013 Sep 2011.

32. Wendel CS, Fotieo GG, Shah JH, Felicetta J, Curtis BH, Murata GH. Incidence of non-severe hypoglycaemia and intensity of treatment among veterans with type 2 diabetes in the U.S.A.: a prospective observational study. Diabet Med 2014;31:1524–31.

33. Farahani P. Sulfonylurea and the Heart: Theoretically a compounded question from a pathophysiological perspec-tive. J Popul Ther Clin Pharmacol 2016;23:e193–e195.

34. Simpson SH, Majumdar SR, Tsuyuki RT, Eurich DT, Johnson JA. Dose-response relation between sulfony-lurea drugs and mortality in type 2 diabetes mellitus: a population-based cohort study. CMAJ 2006;174:169–74.

35. Yeh JS, Sung SH, Huang HM et al. Hypoglycemia and risk of vascular events and mortality: a systematic review and meta-analysis. Acta Diabetol 2016;53:377–92.

36. Soydan N, Bretzel RG, Fischer B, et al. Reduced capacity of heart rate regulation in response to mild hypoglycemia induced by glibenclamide and physical exercise in type 2 diabetes. Metabolism 2013;62:717–24.

37. Chow E, Bernjak A, Williams S et al. Risk of cardiac arrhythmias during hypoglycemia in patients with type 2 diabetes and cardiovascular risk. Diabetes 2014;63:1738–47.

38. Endocrinenews.org. HYPOGLYCEMIA QUALITY COLLABORATIVE STRATEGIC BLUEPRINT. http://endocrinenews endocrine org/wp-content/uploads/HQC_Strategic_Blueprint_VIEW pdf 2016.JPTCP_24_2_2017_Farahani_3_edited.indd 85/23/2017 4:21:22 PM