Original Research
DOI: 10.22374/1710-6222.24.2.6

NON-SEVERE HYPOGLYCEMIA RISK DIFFERENCE BETWEEN SULFONYLUREA AND SODIUM-GLUCOSE COTRANSPORTER-2 INHIBITORS (SGLT2-I) AS AN ADD-ON TO METFORMIN IN RANDOMIZED CONTROLLED TRIALS

By Pendar Farahani, MD, MSc, FRCPC, DABIM, FACP, FACE

Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada. Programs for Assessment of Technology in Health (PATH), Hamilton, ON, Canada.

Correspondence: farahanp@mcmaster.ca

Submitted: February 2, 2017. Accepted May 16, 2017. Published: May 23, 2017.

ABSTRACT

Background
Non-severe hypoglycemia reduces well-being, lowers quality of life, reduces productivity and increases treatment costs. The non-severe hypoglycemia rate, attributable to sulfonylurea (SU) utilization compared with newer classes such as SGLT2-I, could be of clinical significance.

Objective
To explore the non-severe hypoglycemia risk difference (RD) for SU use compared with SGLT2-I in randomized controlled trials (RCTs) as an add on to metformin.

Methods
A search was conducted for RCTs of SGLT2-I. The PubMed database was utilized for this search. The search was limited to RCTs reported in English language for canagliflozin, dapagliflozin, and empagliflozin. SU dose comparison was utilized to convert the dose of SUs to glimepiride equivalent doses.

Results
In total, 118 RCTs were reviewed; 6 articles had an arm for a SU as add on to metformin. Six articles belong to 3 RCTs, which reported results for 52 weeks and 104 weeks. Average non-severe hypoglycemia rate for SU arm was 30% (5.5%) [Mean (SD)] for 52 weeks and 35.6% (6.1%) for 104 weeks. RD for non-severe hypoglycemia events for SU compared to SGLT2-I was 26.7% (4.9%) for 52 weeks (*p*-value less than 0.001) and 30.6% (5.5%) for 104 weeks (*p*-value less than 0.001). There was a significant correlation between dose of SU and hypoglycemia rate (Pearson correlation 0.995; R-square 99%).

Conclusion
This study illustrated that a large proportion of patients who had exposure to SU in RCTs of SGLT2-I experienced non-severe hypoglycemia compared to SGLT2-I. There was a close relation between SU dose and increased probability of non-severe hypoglycemia events.

Keywords: *diabetes, sulfonylurea, SGLT2-I, hypoglycemia, risk*

BACKGROUND

Sulfonylureas (SUs) are associated with documented effective glucose lowering outcomes, low cost and decades of clinical experience in diabetes management.[1] However, SU usage is associated with the risk of hypoglycemia, both severe and non-severe.[1] Both severe and non-severe hypoglycemia are associated with a lower health-related quality of life and an increased burden of disease.[2–5] Non-severe hypoglycemia reduces well-being and lowers quality of life by increasing anxiety and fear of repeated events, which can lead to negative lifestyle changes, driving concerns, and reduced work productivity.[6,7] In general, severe hypoglycemia is defined as an episode of low blood glucose where a patient requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions; otherwise, an episode of low blood glucose can be categorized as non-severe.[8–10]

Currently, more than 10 classes of medication are available for diabetes pharmacotherapy.[8,10] Each class of medication has its own advantages and disadvantages from an efficacy and safety profile perspective.[8,10] In this milieu, enhanced individualized and patient-centred pharmacotherapy for diabetes is becoming more attainable than ever before.[9] Newer classes of medications such as glucagon-like peptide 1 (GLP-1) receptor agonists, dipeptidyl peptidase 4 (DPP-4) inhibitors and SGLT2-I may reduce the risk of hypoglycemia. Non-severe hypoglycemia rate, attributable to SU utilization compared to newer classes such as SGLT2-I could be of clinical significance. The objective of this study was to explore the rate of non-severe hypoglycemia attributable to SU use in RCTs of SGLT2-I.

METHODS

A search of the PubMed database was conducted for randomized controlled trials (RCTs) of SGLT2-I. The search date was set for published studies prior to January 15th, 2016. The search was limited to RCTs reported in English language for "canagliflozin," "dapagliflozin," and "empagliflozin." RCTs were selected that had at least one arm of SU versus SGLT2-I as an add-on to metformin. The following data were extracted from studies that met the inclusion criteria: rate of non-severe hypoglycemia, duration of study, type and dose (average mg/day) of SU and SGLT2-I. The ClinicalTrials.gov registry was searched for further data as required. Comparative daily dose for SU was utilized to convert the dose of SUs to glimepiride equivalent doses (Table 1).[11]

The non-severe hypoglycemia rates at 52 weeks and 104 weeks were obtained for both SU arm and SGLT2-I arm. Of note, insulin was not used and was not reported for any arms of these RCTs. Although the definition of hypoglycemia episodes among selected RCTs were not exactly the same (Appendix 1), they were very similar for defining severe versus non-severe hypoglycemia. All of them followed and incorporated the general definition of severe hypoglycemia as an episode of low blood glucose where a patient requires assistance of another person.

Risk difference (RD) was calculated for the difference between SU arm and SGLT2-I arm for non-severe hypoglycemia rates. The Chi-square test was utilized for inferences of non-severe hypoglycemia rates. Correlation between dose of SU as glimepiride equivalent doses (mg per day) and non-severe hypoglycemia rates was calculated utilizing Pearson's correlation. Non-severe hypoglycemia rates modelled against glimepiride equivalent doses as average daily dose for 52 and 104 weeks. All data were reported as mean (SD) using Minitab 17 software for data analysis.

RESULTS

Totally, 118 RCTs reports were reviewed (canagliflozin 44 RCTs, dapagliflozin 48 RCTs, and empagliflozin 26 RCTs) (Appendix 2). Six reports had an arm for SU as add on to metformin[12-17]. These 6 reports belong to 3 RCTs, which reported results for 52 weeks and 104 weeks (Table 2). In these trials, the average age of participants was 56 (1.5) years-old, the average duration of diabetes at baseline was

Table 1 Sulfonylurea Comparative Daily Dose

Glimepiride (*Amaryl*, generics)	1 mg QD	1 mg to 2 mg QD	2 mg QD	4 mg QD	8 mg QD
Glipizide (*Glucotrol*, generics)	2.5 mg QD	5 mg QD or divided BID	5 mg QD or divided BID	10 mg QD or divided BID	20 mg to 40 mg Divided BID
Glipizide extended-release (*Glucotrol XL*, generics)	2.5 mg QD	5 mg QD	5 mg QD	10 mg QD	20 mg QD
Glyburide (*Diabeta*, *Micronase*, generics)	1.25 mg QD	2.5 mg to 5 mg QD or divided BID	5 mg QD or divided BID	10 mg QD or divided BID	20 mg QD or divided BID
Glyburide, micronized (*Glynase PresTab*, generics)	0.75 mg QD	1.5 mg to 3 mg QD or divided BID	3 mg QD or divided BID	6 mg QD or divided BID	12 mg QD or divided BID

BID = twice per day. QD = daily.

6.5 (0.5) years and the average body mass index for patients was 30.5 (0.5) (Table 2).

Average non-severe hypoglycemia rate for SU arm was 30% (5.5%) over 52 weeks and 35.6% (6.1%) over 104 weeks. However, average non-severe hypoglycemia rate for SGLT2-I arm was much lower than SU arm at the level of 3.3% (1.0%) over 52 weeks and 4.9% (1.6%) over 104 weeks (Figure 1). RD for non-severe hypoglycemia events to SU compared to SGLT2-I was 26.7% (4.9%) for 52 weeks (p-value less than 0.001) and 30.6% (5.5%) for 104 weeks (p-value less than 0.001).

Average SU dose as glimepiride equivalent doses was 4.93 (1.99) mg/day. There was a significant correlation between dose of SU as glimepiride equivalent doses and non-severe hypoglycemia event rate (Pearson correlation 0.995; R-square 99%) (Figure 2). This association was mathematically modelled as follows: non-severe hypoglycemia event rate is equal to [5.38% + 5.31% x average dose of glimepiride equivalent (mg/day)] over 52 weeks and [8.83% + 5.70% x average dose of glimepiride equivalent (mg/day)] over 104 weeks.

DISCUSSION

The current study illustrates that a large proportion of patients (about one-third) who had exposure to SU in RCTs of SGLT2-I experienced non-severe hypoglycemia events. The rate of non-severe hypoglycemia events attributable to SGLT2-I exposure in the RCTs was very low. Therefore, the absolute RD was significantly large (more that 25%). A large proportion of patients in these RCTs were elderly and obese. The data are applicable to Canadian population with type 2 diabetes.

In recent years, the highest increase in the number of individuals with diabetes in Canada was seen in the 60 to 64 year old age group. The aging population is the most important demographic change affecting diabetes prevalence worldwide.[18] Diabetes in

TABLE 2 Extracted Data from Selected RCTs on SGLT2-I versus SU as an Add-On to Metformin

SGLT2-I Versus SU (+MET)	Duration of RCT	Number of patient in SU arm	Mean age	BMI	Mean duration of type 2 diabetes	Percentage of patients with non-severe hypoglycemia in SU arm	Average dose (mg/day) for SU in RCT	Percentage of patients with non-severe hypoglycemia in SGLT2-I arm
Dapagliflozin versus Glipizide[12]	52-week	n = 408	58.4	31.2 ± 5.1	7 ± 6	39%	glipizide = 16.4 (6.56) mg/day (MAX: 40 mg/d)	3.4%
Dapagliflozin versus Glipizide[13]	104-week	n = 408	58.4	31.2 ± 5.1	6.3 years	45.1%	glipizide = 16.4 (6.56) mg/day (MAX: 40 mg/d)	4.2%
Canagliflozin versus Glimepiride[14]	52-week	n = 482	56.3 ± 9.0	30.9 ± 5.5	6.6 ± 5.0	31%	Glimepiride = 5.6 (2.3) mg/day (MAX: 8 mg/d)	5%
Canagliflozin versus Glimepiride[15]	104-week	n = 482	56.3 ± 9.0	30.9 ± 5.5	6.6 ± 5.0	37.6%	Glimepiride = 5.6 (2.3) mg/day (MAX: 8 mg/d)	8.2%
Empagliflozin versus Glimepiride[16]	52-week	n =780	55.7 (10.4)	30.11 (5.59)	6.1 years (estimated)	20%	Glimepiride: 2.7 mg/daily (MAX: 8 mg/d)	1.5%
Empagliflozin versus Glimepiride[17]	104-week	n =780	55.7 (10.4)	30.11 (5.59)	6.1 years (estimated)	24.2%	Glimepiride: 2.7 mg/daily (MAX: 8 mg/d)	2.5%

BMI = body mass index; SU = sulfonylurea; RTC = randomized control trials.

FIG. 1 Rate of non-severe hypoglycemia for SU and SGLT2-I.

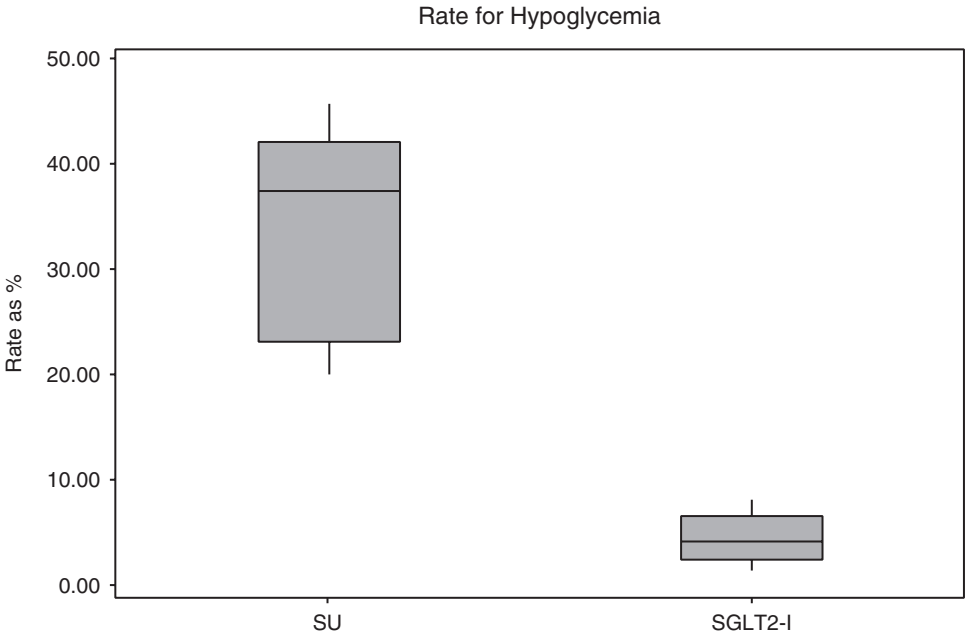
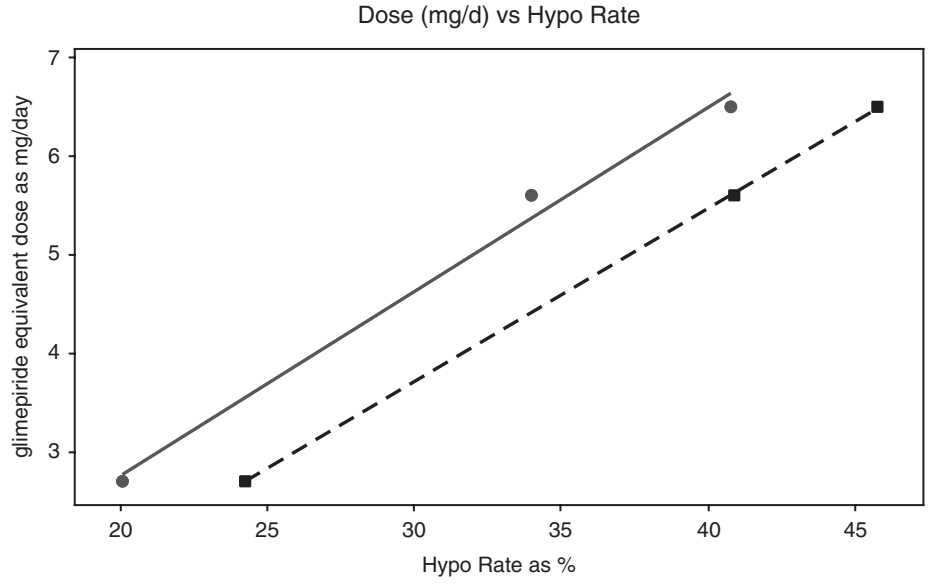


FIG. 2 Correlation between dose of SU and hypoglycemia rate.



Bold line: Hypo Rate at 52 weeks - Dash line: Hypo Rate at 104 weeks

the elderly is metabolically distinct from diabetes in younger people and the approach to therapy should be different.[8] With overwhelming demographic trends of aging one of the most important factors in diabetes pharmacotherapy should stem from avoidance of hypoglycemia, particularly in the elderly and patients with cardiac disease. This includes both severe and non-severe episodes.

This is an important public health issue in Canada, as non-severe hypoglycemic events can be impactful in elderly population in Canada with increased risk of fragility. The aging of the Canadian population has been one of the factors contributing to the increase in the number of Canadians living with diagnosed diabetes.[19–21]

Non-severe hypoglycemia events can lead to cognitive dysfunction and frailty in older persons.[22] The incidence of hypoglycemia in people over age 75 with diabetes is difficult to estimate due to the limited number of clinical studies and the lack of standardization in hypoglycemia diagnosis.[22] Recurrent episodes of non-severe hypoglycemia are associated with significant chronic consequences leading to physical and cognitive dysfunction and eventually frailty and disability.[22]

A report from the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) found that for the 2013 calendar year, for 6,150 patients who had prescribed SU, average age was 65.4 years. This means more than half of patients exposed to SU were older adults. Established atherosclerotic cardiovascular disease was observed in 16.8% of the patients with 13.2% having ischemic heart disease or myocardial infarction or coronary artery disease.[23] Also, CPCSSN data demonstrated that 40% of primary care patients in the database were prescribed SU in their anti-hypoglycemic regimen in their electronic medical record over a 2-year period between January 1, 2011 and December 31, 2012.[24] SU represented the next largest class of medications after metformin.

Non-severe hypoglycemia events frequently occur in real-world clinical settings but are infrequently reported. A survey study from 7 European countries reported a high proportion of respondents rarely or never informed their general practitioner or specialist about hypoglycemia: 65% in type 1 diabetes and 50–59% in type 2 diabetes.[25] This study concluded that non-severe hypoglycemic events are common among people with diabetes in real-world settings, however, many rarely or never inform their general practitioner or specialist about their hypoglycemia and the real burden of hypoglycemia may be underestimated.[25]

In the European study, overall, 2.3% and 8.9% of non-severe hypoglycemia events in patients with type 1 and type 2 diabetes, respectively, resulted in contact with a health care professional.[26] In a US study, non-severe hypoglycemia was only reported by 25% of patients to a health care professional after an episode.[27]

A Danish survey reported the annual rate for non-severe hypoglycemic events in insulin-treated diabetic patients.[28] In this study, the mean annual rate for non-severe hypoglycemic events was 99 in type 1 diabetes and 27 in type 2 diabetes per patient. Type 1 diabetes patients reported approximately 22 nocturnal non-severe hypoglycemic events per year and type 2 diabetes patients reported 8 nocturnal non-severe hypoglycemic events per year. Overall, 64% of type 1 diabetes and 51% of type 2 diabetes patients rarely or never informed health care professionals about non-severe hypoglycemic events.[28] Patients from other European countries such as Germany[29] and Austria[30] reported similar results.

Non-severe hypoglycemia events impact quality of life and well-being. In the survey study from 7 European countries, patients reported feeling tired, irritable, and having negative feelings following non-severe hypoglycemia events.[26] After non-severe hypoglycemia events, 59% of patients reported feeling tired or fatigued and 25% reported reduced alertness.[28] The negative effects on patients' emotional well-being lasted for 5 hours on average after non-severe hypoglycemia events.[28]

Subsequently, non-severe hypoglycemia events that impact work productivity lead to increased costs of diabetes care. In the European survey, among respondents who were employed (48%), loss of work time after the last hypoglycemic event was reported for 9.7% of non-severe hypoglycemia events. Overall, 10.2% (daytime) and 8% (nocturnal) non-severe hypoglycemia events led to work time loss.[26] The mean of work time loss was 84.3 minutes for daytime and 169.6 minutes for nocturnal non-severe hypoglycemia episodes.[26] In another study, among employed patients, 9% of non-severe hypoglycemia events led to an average lost work time of 1.4 hours in type 1 diabetes and 1.9 hours in type 2 diabetes per event.[28]

In a US study,[27] non-severe hypoglycemia reduced productivity with an average productivity loss of $2,300 per person per year. After a nocturnal non-severe hypoglycemia events, 23% of patients arrived late or missed work, 32% of patients missed a meeting or did not finish a task on time and 15 hours of work was lost.[27]

Across European countries, there was a mean increase in blood glucose test use of 3 tests in the week following a non-severe hypoglycemia event.[26] In another report, in the week after a non-severe hypoglycemia event, blood glucose measurement increased by 8% in type 1 diabetes and 21% in type 2 diabetes.[28] In the US, non-severe hypoglycemia increased treatment cost with blood glucose testing which went up by 5.6 extra tests within 7 days after a non-severe hypoglycemia episode.[27]

Despite evidence, most economic models in Canada do not capture and do not incorporate the impact of non-severe hypoglycemia on quality of life and related costs. Particularly, economic evaluation from public payers' perspective such as CADTH (Canadian Agency for Drugs and Technologies in Health) only incorporate severe hypoglycemia episodes in their economic modelling, which is important from the public payer perspective. Non-severe hypoglycemia, which is important from patients' perspective, is ignored.[31]

This study demonstrated that there is a close relation between SU dose and increased probability of non-severe hypoglycemic events in these RCT settings. Studies from real-world clinical settings reflected similar evidence. A prospective observational study among veterans with type 2 diabetes in the US illustrated a significant association between increased frequency of non-severe hypoglycemic events and an increased likelihood of SU dose.[32]

The relationship between severity of hypoglycemia and increased cardiovascular events with SU utilization is controversial.[23,33] A population-based cohort study found dose–response relation between SU drugs and mortality in type 2 diabetes.[34] Simpson and colleagues published an analysis of administrative data for 4,138 patients with type 2 diabetes taking glyburide monotherapy and 1,537 patients taking metformin monotherapy.[34] The authors found that an association between higher daily doses and increased risk of death existed with the use of glyburide.[34] A meta-analysis illustrated a dose-dependent relationship between the severity of hypoglycemia and adverse vascular events and mortality.[35] Hazard ratio (HR) for mild hypoglycemia was 1.68 (*p*-value less than 0.001) and HR for severe hypoglycemia was 2.33 (*p*-value less than 0.001)[35].

A physiological study in type 2 diabetes illustrated that heart rate variability decreased in response to mild hypoglycemia induced by glibenclamide and physical exercise in type 2 diabetes.[36] Reduced capacity of heart rate regulation or decreased heart rate variability was associated with enhanced mortality due to abnormal cardiac rhythm.[36] Furthermore, Chow and colleagues[37] in an observational study of patients with type 2 diabetes simultaneously utilized outpatient Holter monitors and continuous interstitial glucose monitors. The authors observed that hypoglycemia was associated with possible ischemic changes (T-wave flattening), repolarization defects (increased QT intervals corrected for heart rate), and various cardiac arrhythmias.[37]

The limitations of this study are as follows. Defining and reporting hypoglycemia events were similar among these 3 RCTs; however, were not exactly the same (see Appendix 1). Future clinical guidelines should be developed for comprehensive definition and reporting of hypoglycemia episodes, both severe and non-severe, in RCTs and real-world clinical settings[38]. There is an urgent need for developing policies and frameworks to address hypoglycemia due to pharmacotherapy in diabetes care.[38] The initiatives are already underway with scientific organizations such as The Endocrine Society to address this issue.[38] Furthermore, future comprehensive research studies should be conducted on pathophysiology and adverse outcomes of non-severe and severe hypoglycemia from clinical and economic perspectives.

Another limitation of this study stems from the lack of access to individual patient level data. For this study only average and summary data was available through published studies, which by itself limits the ability to conduct further detailed analysis and data interpretation.

In conclusion, this study illustrates that a large proportion of patients who had exposure to SU as

add on to metformin in RCTs experienced non-severe hypoglycemia compared to SGLT2-I as add on to metformin. In clinical practice for patient-centred diabetes care, the choice of pharmacotherapy and negative impacts of non-severe hypoglycemia on quality of life, economic and clinical outcomes should be considered.

SOURCE OF FUNDING

This study was supported by a research grant from AZ Canada.

CONFLICT OF INTEREST

Research grants and consulting: AZ Canada.

REFERENCE LIST

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. Hypoglycemia: 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 diabetes--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 versus 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. Durability 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 reduction 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 gov/ct2/show/study/NCT01167881?term=NCT01167881&rank=1 2016.
17. Ridderstrale M, Andersen KR, Zeller C, et al. Comparison 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.

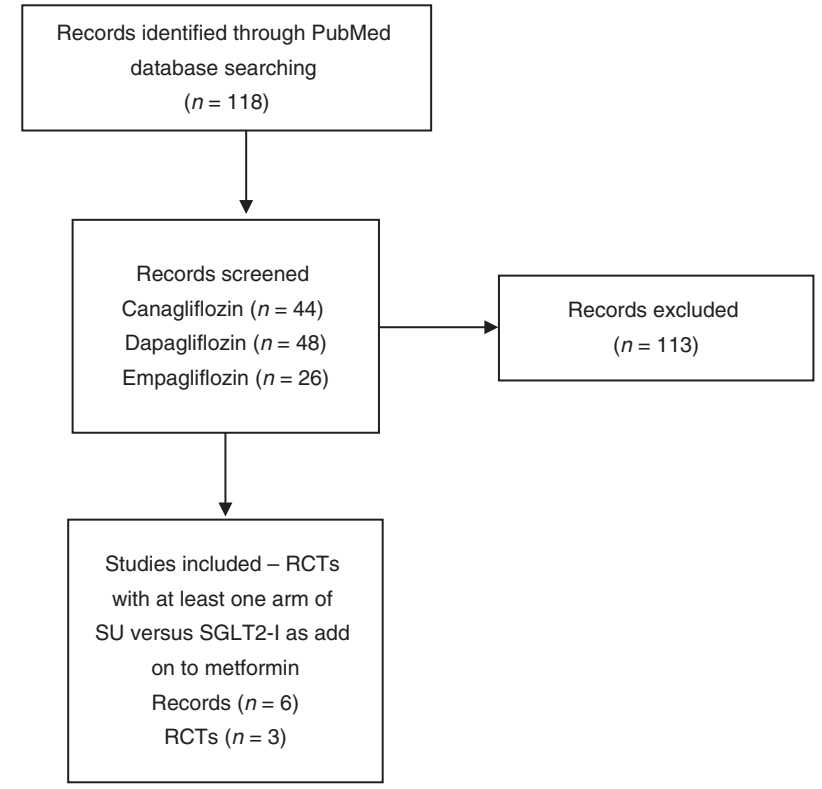
18. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27:1047-1053.
19. Canadian Diabetes Association. An economic tsunami: the cost of diabetes in Canada. http://www diabetes ca/ economic report/ [serial 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 recognized risk factor for frailty. Aging Dis 2015;6:156–67.
23. Farahani P, Khan S, Oatway M, Dziarmaga A. Exploring the distribution of prescription for sulfonylureas in patients with type 2 diabetes according to cardiovascular 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, Weitgasser 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 frequency and impact of non-severe hypoglycemic events in insulin-treated diabetic patients in Denmark. Diabetes Management 2015;5:67–78.
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 perspective. J Popul Ther Clin Pharmacol 2016;23:e193–e195.
34. Simpson SH, Majumdar SR, Tsuyuki RT, Eurich DT, Johnson JA. Dose-response relation between sulfonylurea 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.

APPENDIX 1 Definition of Hypoglycemia Episodes amongst Selected Randomized Control Trials

The canagliflozin study reported documented hypoglycaemic episodes, including biochemically documented episodes (concurrent finger stick glucose or plasma glucose ≤3.9 mmol/L with or without symptoms) and severe episodes (those needing assistance of another individual or resulting in seizure or loss of consciousness). The empagliflozin study reported confirmed hypoglycaemic adverse events as plasma glucose ≤3.9 mmol/L or requiring assistance. The dapagliflozin study defined major hypoglycemia as a symptomatic episode requiring external assistance due to severely impaired consciousness or behavior, with capillary or plasma glucose levels of 54 mg/dL (3.0 mmol/L) and recovery after glucose or glucagon administration. Minor hypoglycemia was defined as a symptomatic episode with capillary or plasma glucose levels of 63 mg/dL (3.5mmol/L), irrespective of the need for external assistance, or an asymptomatic episode with capillary or plasma glucose levels of 63 mg/dL (3.5 mmol/L) that did not qualify as a major episode. Other hypoglycemia was defined as an episode with symptoms suggestive of hypoglycemia but without measurement confirmation.

Data from Nauk et al,[12,13] Cefalu et al,[14] Leiter et al,[15] and ClinicalTrials.gov.[16]

APPENDIX 2 PRISMA Flow Diagram



SU = sulfonylurea; RCTs = randomized control trials.