RESEARCH LETTER

Estimated population-level benefits of sodium-glucose cotransporter-2 inhibitors introduction in the Polish population

Gracjan Iwanek, Robert Zymliński, Piotr Ponikowski, Jan Biegus

Institute of Heart Diseases, Wroclaw Medical University, Wrocław, Poland

Introduction Almost a decade ago the investigators of the EMPA-REG OUTCOME[1] trial reported that empagliflozin (sodium-glucose cotransporter-2 [SGLT-2] inhibitor), a glucose-lowering drug, not only reduced the occurrence of the primary cardiovascular end point but also significantly (by 35%) reduced the incidence of heart failure hospitalizations (HFHs) in high-risk type 2 diabetes mellitus (T2DM) population.[2] Since then, this effect has been confirmed and repeated in a broad spectrum of patients with and without DM. Moreover, for the last few years, we have been witnessing gradual extension of the indications for SGLT-2 inhibition, as SGLT-2 inhibitors have been shown to be beneficial in a broad spectrum of diseases (T2DM, HF, and chronic kidney disease [CKD]). According to the latest results of the DELIVER[3] (Dapagliflozin Evaluation to Improve the Lives of Patients With Preserved Ejection Fraction Heart Failure) and EMPEROR-Preserved[6] (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) trials, SGLT-2 inhibitors improve the outcomes in a wide spectrum of HF patients, irrespectively of their left ventricular ejection fraction (LVEF).

The populations that may potentially benefit from the SGLT-2 inhibitors are of key importance from the clinical and public health standpoints for 2 main reasons. Firstly, the calculated relatively low number needed to treat (NNT) with SGLT-2 inhibitors should, at least theoretically, translate into considerable clinical benefit and substantial reduction in cardiovascular deaths and hospitalizations. Secondly, the target populations are patients suffering from civilizational diseases with very high prevalence, such as T2DM, HF, and CKD.

Our study aimed to quantify the estimated benefit (in terms of mortality and prevention of HFHs) from the initiation of SGLT-2 inhibitors in all potential patients with T2DM, CKD, and HF in the Polish population.

Patients and methods We utilized epidemiologic data from the Polish Ministry of Health for the year 2021[4] to estimate the number of Polish patients with indications for SGLT-2 inhibitors. We adjusted the population size for inclusion criteria and potential overlap between the studied groups. Furthermore, we analyzed data from several clinical trials, including DAPA-HF[5] (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure), DELIVER, EMPEROR, DECLARE-TIMI 58[8] (Dapagliflozin Effect on Cardiovascular Events-Thrombolysis in Myocardial Infarction 58), DAPA-CKD[9] (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease), and EMPA-KIDNEY[10] (Empagliflozin Outcome Trial in Patients with Chronic Kidney Disease) to obtain the calculated NNT. Where it was not applicable, we calculated NNT using the GraphPad Prism software (GraphPad Software, San Diego, California, United States). Finally, based on the available data, we assessed the potential number of prevented outcomes for eligible patients in the Polish population. To calculate the CI, we relied on the NNT and 95% CIs provided by the analyzed studies.

Ethics Our work was based on existing research studies and did not involve direct patient interaction or data collection. As a result, it did not require institutional review board approval or ethics committee oversight. Therefore, obtaining written informed consent from patients was not necessary for our analysis.

Results **Heart failure** There is an estimated number of 741582 patients with HF in the Polish population. As many as 336455 of them (45%) are patients suffering from HF with reduced ejection fraction (HFrEF), and 405126 (55%) from heart failure with preserved ejection fraction (HFpEF).

Correspondence to:
Gracjan Iwanek, MD,
Institute of Heart Diseases,
Wroclaw Medical University,
ul. Borowska 213, 50-566 Wroclaw,
Poland, phone: +48 71 733 11 12,
email: giwanek95@gmail.com
Received: May 15, 2023.
Revision accepted: June 26, 2023.
Published online: July 4, 2023.
Pol Arch Intern Med. 2023;
133 (7-8): 16524
doi:10.20452/pamw.16524

TABLE 1 The estimated number of prevented outcomes after introduction of sodium-glucose cotransporter-2 inhibitors in all eligible patients in the Polish population

Outcome	Study name	Median follow-up time, y	NNT (95% CI)	Estimated number of patients meeting the trial criteria in the Polish population	Estimated number of potentially prevented cases (95% CI)
HF					
CV death	DAPA-HF + DELIVER[5]	1.8	68 (38–280)	741 582	10 906 (2649–19 515)
ACM			67 (36–600)		11 068 (1236–20 600)
Total HF hospitalizations			17 (14–22)		43 622 (33 708–52 970)
First HF hospitalization			32 (22–48)		23 174 (15 450–33 708)
CV death or HF hospitalization			26 (19–41)		28 522 (18 087–39 031)
CV death or HF hospitalization	EMPEROR–preserved[6]	2.2	31 (20–71)	405 126	13 069 (5705–20 256)
HF hospitalization			32 (22–63)		12 660 (6431–18 415)
CV death or HF hospitalization	EMPEROR–reduced[7]	1.3	19 (13–37)	336 455	17 708 (9093–25 881)
HF hospitalization			20 (13–35)		16 823 (9613–25 881)
T2DM and HFrEF					
CV death	DECLARE-TIMI 58[8]	4.2	19 (10–120)	232 181	12 220 (1935–23 218)
ACM			14 (8–54)		16 584 (4300–29 023)
CV death or HF hospitalization			12 (7–49)		19 348 (4738–33 169)
CKD					
Sustained eGFR, declined ESKD, CV or renal death	DAPA-CKD[9]	2.4	19 (15–27)	186 900	12 220 (1935–23 218)
Progression of kidney disease or CV death	EMPA-KIDNEY[10]	2.0	35 (23–73)	186 900	5440 (2560–8126)

Abbreviations: ACM, all-cause mortality; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; NNT, number needed to treat; T2DM, type 2 diabetes mellitus

Type 2 diabetes mellitus The Polish population comprises approximately 2324596 patients suffering from T2DM. The overlap with HF is 22% (511411 patients). The final number of T2DM patients eligible for SGLT-2 inhibitors is 1813115.

Chronic kidney disease The estimated number of patients with CKD in the Polish population is 238000, 11% of them (23100) suffer also from HF, and the number of patients with end-stage CKD is 28000. The final number of CKD patients eligible for SGLT-2 inhibitors is 186900.

Total estimated number of patients eligible for sodium--glucose cotransporter-2 inhibitors in Poland After adjustments for inclusion criteria and potential overlap, the estimated number of patients eligible for SGLT-2 inhibitors in the Polish population is 2741667.

The estimated number of outcomes potentially prevented by sodium-glucose cotransporter-2 inhibitors In TABLE 1 we present the estimations of potentially prevented outcomes in HF, T2DM, and CKD, if all eligible patients received an SGLT-2 inhibitor, at the population level. In brief, the SGLT-2 inhibitor treatment in all HF patients should translate into 10906 (95% CI, 2649–19515) fewer cardiovascular deaths during the median 1.8 years of follow-up (IQR, 1.4–2.5), and by 43622 (95% CI, 33708–52970) lower number of HF hospitalizations. Similarly, the treatment should prevent 12220 (95% CI, 1935–23218) cardiovascular deaths in the patients with T2DM.

Discussion Concerning the new recommendations in Poland, there are 2741667 patients eligible for SGLT-2 inhibitor therapy. The most accurate data are available for HF. The DELIVER and EMPEROR studies have confirmed the effectiveness of this therapy in this patient population, irrespective of LVEF value, with a significant reduction in key end points.

Broad application of SGLT-2 inhibitors in HF can prevent approximately 11068 deaths of any cause, 10906 deaths from cardiovascular causes, and 43622 HFHs, including 23174 first-time hospitalizations, within a median period of about 1.8 years (IQR, 1.4–2.5) at the population level. These numbers have significant implications in not only medical but also societal terms, with associated improvements in the patient quality of life, reduced treatment costs, and a decrease in premature deaths in the Polish population.

To our knowledge, this is the first time the analysis has been expanded to include patients with T2DM and CKD, where the use of SGLT-2 inhibitors provides tangible benefits.

Due to the lack of accurate epidemiologic data, our analysis is only an estimation. Therefore, the final numbers of prevented outcomes are based on the patients meeting the inclusion criteria of specific clinical trials. Probably a larger number of patients is eligible for SGLT-2 inhibitor

therapy based on the current knowledge. Additionally, epidemiologic data rely on registries of reported patients, which may significantly differ from the actual number of patients with the given condition. Despite the lack of information regarding the coexistence of HF, T2DM, and CKD in Poland, we suspect that our data are underestimated, and the benefits of incorporating SGLT-2 inhibitors in therapy may be even bigger in the Polish population at large.

Limitations The study is not free from limitations. Our analysis does not provide precise data and is only an estimation. The final number of patients benefiting from the inclusion of SGLT-2 inhibitors may vary. Despite reaching out to the appropriate government bodies, obtaining the exact number of patients with HF, T2DM, and CKD in Poland was not feasible. The ratio of patients with HF and reduced vs preserved LVEF was estimated based on available population studies.

ARTICLE INFORMATION

ACKNOWLEDGMENTS We acknowledge the Wroclaw Medical University for providing a platform to conduct this study and prepare this manuscript.

FUNDING This research was financially supported by a statutory grant to the Institute of Heart Diseases, Wroclaw Medical University, Poland (SUBZ.A460.23.005).

CONFLICT OF INTEREST None declared.

HOW TO CITE Iwanek G, Zymliński R, Ponikowski P, Biegus J. Estimated population-level benefits of sodium-glucose cotransporter-2 inhibitors introduction in the Polish population. Pol Arch Intern Med. 2023; 133: 16524. doi:10.20452/pamw.16524

REFERENCES

1 Bernard Z, Christoph W, John M. L, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015; 373: 17-18.

2 Ferrannini E, Mark M, Mayoux E. CV Protection in the EMPA-REG OUTCOME trial: a "thrifty substrate" hypothesis. Diabetes Care. 2016; 39: 1108-1114.

3 Solomon SD, de Boer RA, DeMets D, et al. Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER trial. Eur J Heart Fail. 2021; 23: 1217-1225.

4 Ministry of Health. Maps of health needs. Epidemiology (Statistics Poland and National Health Fund) [in Polish]. https://basiw.mz.gov.pl/mapy-informacje/mapa-2022-2026/analizy/epidemiologia/epidemiologia-wersja-polska-gus-i-nfz/. Accessed February 6, 2023.

5 Jhund PS, Kondo T, Butt JH, et al. Dapagliflozin across the range of ejection fraction in patients with heart failure: a patient-level, pooled meta-analysis of DAPA-HF and DELIVER. Nat Med. 2022; 28: 1956-1964.

6 Anker SD, Butler J, Filippatos G, et al. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2021; 385: 1451-1461.

7 Packer M, Anker SD, Butler J, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. N Engl J Med. 2020; 383: 1413-1424.

8 Verma S, Mcmurray JJV. The serendipitous story of SGLT2 inhibitors in heart failure: new insights from DECLARE-TIMI 58. Circulation. 2019; 139: 2537-2541.

9 Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020; 383: 1436-1446.

10 Colin B, Martin JL, Christoph W, et al. Empagliflozin in patients with chronic kidney disease. N Engl J Med. 2023; 388: 117-127.