#01/2022
ISSN 2299-1247

JHPOR | Journal of Health Policy & Outcomes Research

SGLT2 inhibitors and cardioprotection. Literature review and real-world data from Poland

DOI:10.7365/JHPOR.2022.1.1

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Keywords:

cardioprotection, cardiovascular events, diabetes, real-world data, reimbursement, SGLT2

How to cite this article?
Seweryn M., Rękawek B., Agustyńska J., SGLT2 inhibitors and cardioprotection. Literature review and real-world data from Poland J Health Policy Outcomes Res [Internet]. 2022[cited YYYY Mon DD];2. Available from: https://www.jhpor.com/article/2275-sglt2-inhibitors-and-cardioprotection-literature-review-and-real-world-data-from-poland

contributed: 2021-10-19
final review: 2022-01-14
published: 2022-01-23

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Abstract

Background

Sodium-glucose cotransporter-2 (SGLT2) has been demonstrated to reduce cardiovascular events in randomized controlled settings. This group of drugs has been reimbursed for a selected group of patients in Poland since 2019. A decision to extend the reimbursement would be considered after analyzing the real-world data of the SGLT2 in Polish conditions. The aim of this study was the assessment of current evidence, both from the literature and real data from the health care system.

Methods

The targeted literature review was made based on high-quality articles on the topic of interest. Randomized clinical trials and publications based on real-world data were collected. Collaterally, data from the Polish third-party payer, National Health Fund (NHF), for 2020 was gathered.

Results

Ten publications were included in the final analysis. They showed that the use of cardioprotectors in the treatment reduces cardiovascular events and lowers the rate of hospitalization for heart failure, regardless of pre-existing CVD or diabetes.

Having regard the NHF data from Lesser Poland, in SGLT2 group, there were 196 out of 5,332 patients hospitalized due to cardiovascular incidents (3.68%). This percentage is lower than in the whole insulin group (5.06%) and close to the subgroup who started therapy in a similar period as SGLT2 group (5.07%).

Conclusions

SGLT2 significantly affects the treatment of cardiovascular events across the countries reported in the literature. Our study, the first real-world evidence from Poland, proves the cardioprotective effect of these groups of drugs as well. The main limitation is data restricted to one region, thus future studies with whole country coverage are needed.

Introduction

About 422 million people worldwide have diabetes and each year 1.6 million deaths are directly attributed to this disease; both the number of cases and the prevalence of diabetes have been increasing steadily over the past few decades. For people living with diabetes, access to affordable treatment, including insulin, is critical to their survival.[1] According to the data published by the National Health Fund (NHF),[2] in 2013 almost 2,507,000 people suffered from diabetes in Poland. In 2019, this number increased to over 2,985,000, which shows how dynamic growth we are dealing with. According to the guidelines of the Polish Diabetes Association,[2] pharmacotherapy reducing hyperglycemia is of the key importance in preventing and inhibiting the progression of chronic diabetes complications, mainly cardiovascular. In 2019, 2.99 million people in Poland got their prescription for antidiabetics or blood glucose test strips, and the reimbursement for them amounted to PLN 1.487 billion.[3] Sodium-glucose cotransporter type 2 inhibitors (SGLT2) are a novel type of hypoglycemic agent in increasing urinary glucose and sodium excretion. In many clinical trials, they have been demonstrated to reduce cardiovascular events, particularly heart failure and diabetic kidney disease.[4,5,6,7] Because of the limited financial resources of the National Health Fund, the Polish Ministry of Health decided to reimburse therapy in the first place for the most urgent patients. After positive reimbursement decision, representatives of the Ministry declared that after analyzing the real-world data of the SGLT2 inhibitors in Polish conditions, a decision would be made to extend their reimbursement. Until now, no relevant analyzes have been conducted by the Ministry of Health or NHF on SGLT2 reimbursement benefits. To address these gaps, the authors decided to show evidence from the literature review and real data from the health care system.

Materials and Methods

A literature review conducted on Pubmed was held on September 2021. The selection of literature was divided into two stages. The first group of publications were articles with comparison of cardiovascular events in patients treated with SGLT2 inhibitors and those who received placebo or other glucose-lowering drugs (GLDs). The

second group of chosen publications included the number of treatment with SGLT2 inhibitors in comparison with other GLDs. All selected articles contain current information, they were published after 2015. Moreover, we collected data from NHF for 2020. The main goal was to identify the rate of cardiovascular events in the SGLT2 group and compare it with the group of patients who started taking insulin at a similar time. Insulin long-term users were included as well.

We applied for data to National Health Fund. NHF was requested to report the number of patients with diabetes (ICD-10 codes from E10 to E14) who, from January to December 2020 (SGLT2 reimbursement period), were hospitalized due to the following diagnoses:

- I50 (including I50.0, I50.1, I50.9) - heart failure,
- I21 (including I21.0, I21.1, I21.2, I21.3, I21.4, I21.9) - acute myocardial infarction,
- I22 (including I22.0, I22.1, I22.8) - subsequent myocardial infarction,
- I62 (including I62.0, I62.1, I62.9) - other nontraumatic intracranial hemorrhage,
- I63 (including all codes from I63.0 to I63.9) - cerebral infarction,
- I64 - stroke, not specified as hemorrhage or infarction.

This group included patients who in 2020 filled their prescriptions for reimbursed SGLT2 inhibitors (canagliflozin, empagliflozin, dapagliflozin) and, separately, patients receiving reimbursed prescriptions for insulin.
The data applies to both, insulin long-term users and patients who started taking insulin in a similar period, i.e., not earlier than in the 4th quarter of 2019 or at the beginning of 2020 (no prescription for any insulin in the period from January to October 2019), to compare groups as similar as possible.

Results

Literature review

In Empagliflozin Cardiovascular Outcomes, and Mortality in Type 2 Diabetes[4] the authors presented the results of EMPA-REG OUTCOME trial. This was a randomized, double-blind, placebo-controlled trial to assess the effect of once-daily empagliflozin (at a dose of either 10 mg or 25 mg) versus placebo on cardiovascular events in adults with type 2 diabetes at high cardiovascular risk against a background of standard care. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction (excluding silent myocardial infarction), or nonfatal stroke. The key secondary outcome was a composite of the primary outcome plus hospitalization for unstable angina. Patients were treated at 590 sites in 42 countries. The trial continued until an adjudicated primary outcome event had occurred in at least 691 patients. A total of 7,020 patients were treated (median observation time 3.1 years). The primary outcome occurred in a significantly lower percentage of patients in the empagliflozin group (10.5% of patients) than in the placebo group (12.1% of patients). The key secondary outcome occurred in 12.8% of patients in the empagliflozin group and 14.3% of patients in the placebo group. As compared with placebo, empagliflozin resulted in a significantly lower risk of death from cardiovascular causes, death from any cause, and hospitalization for heart failure. There were no significant differences between groups in the occurrence of myocardial infarction or stroke (Table 1).

The authors concluded that patients with type 2 diabetes at high risk for cardiovascular events who received empagliflozin, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome and death from any cause when the study drug was added to standard care.

In Dapagliflozin and Cardiovascular Outcomes in Type 2 Diabetes[5] the authors reported on the results of DECLARE–TIMI 58 trial. This was a randomized, double-blind, multinational, placebo-controlled, phase 3 trial of dapagliflozin in patients with type 2 diabetes and established atherosclerotic cardiovascular disease or multiple risk factors for atherosclerotic cardiovascular disease. The primary efficacy outcomes were MACE (defined as cardiovascular death, myocardial infarction, or ischemic stroke) and a composite of cardiovascular death or hospitalization for heart failure. Secondary efficacy outcomes were a renal composite (≥40% decrease in estimated glomerular filtration rate to <60 ml per minute per 1.73 m2 of body-surface area, new end-stage renal disease, or death from renal or cardiovascular causes) and death from any cause. Researchers evaluated 17,160 patients, including 10,186 without atherosclerotic cardiovascular disease, who were followed for a median of 4.2 years.

In the primary safety outcome analysis, dapagliflozin met the prespecified criterion for noninferiority to placebo with respect to MACE. In the two primary efficacy analyses, dapagliflozin did not result in a lower rate of MACE but did result in a lower rate of cardiovascular death or hospitalization for heart failure, which reflected a lower rate of hospitalization for heart failure. The results showed that there was no difference between the groups in the rate of cardiovascular death. A renal event occurred in 4.3% in the dapagliflozin group and 5.6% in the placebo group (Table 2).

Table 1. Risk of outcomes for empagliflozin vs placebo group					
Outcome	Empagliflozin n (%)	Placebo n (%)	Hazard ratio	95 % CI	p-value
Primary outcome	490 (10.5)	282 (12.1)	0.86	0.74–0.99	<0.001
Secondary outcome	599 (12.8)	333 (14.3)	0.89	0.78–1.01	<0.001
Death from cardiovascular causes	172 (3.7)	137 (5.9)	0.62	0.49 – 0.77	<0.001
Death from any cause	269 (5.7)	194 (8.3)	0.68	0.57 – 0.82	<0.001
Hospitalization for heart failure	126 (2.7)	95 (4.1)	0.65	0.50 – 0.85	0.002
Fatal or nonfatal myocardial infarction excluding silent myocardial infarction	223 (4.8)	126 (5.4)	0.87	0.70–1.09	0.23
Fatal or nonfatal stroke	164 (3.5)	69 (3.0)	1.18	0.89–1.56	0.26

CI – confidence interval; n (%) – number of patients with outcomes.

Table 2. Risk of outcomes for dapagliflozin vs placebo group				
Outcome	Dapagliflozin n (%)	Placebo n (%)	Hazard ratio	95 % CI
MACE (primary outcome)	756 (8.8)	803 (9.4)	0.93	0.84–1.03
Cardiovascular death or hospitalization for heart failure	417 (4.9)	496 (5.8)	0.83	0.73–0.95
Hospitalization for heart failure	212 (2.5)	286 (3.3)	0.73	0.61–0.88
Death from cardiovascular cause	245 (2.9)	249 (2.9)	0.98	0.82–1.17
Renal composite	370 (4.3)	480 (5.6)	0.76	0.67–0.87
Death from any cause	529 (6.2)	570 (6.6)	0.93	0.82–1.04

CI – confidence interval; MACE - cardiovascular death, myocardial infarction, or ischemic stroke; n (%) – number of patients with outcomes.

Table 3. Risk of outcomes for empagliflozin vs placebo group					
Outcome	Empagliflozin n (%)	Placebo n (%)	Hazard ratio	95 % CI	p-value
Primary outcome (cardiovascular death or hospitalization for heart failure (first event))	361 (19.4)	462 (24.7)	0.75	0.65 – 0.86	<0.001
Total number of hospitalizations for heart failure	388	553	0.70	0.58 – 0.85	<0.001

CI – confidence interval; n (%) – number of patients with outcomes (for secondary outcome n – total number of hospitalizations).

Table 4. Risk of outcomes for dapagliflozin vs placebo group					
Outcome	Dapagliflozin n (%)	Placebo n (%)	Hazard ratio	95 % CI	p-value
Primary composite outcome	197 (9.2)	312 (14.5)	0.61	0.51 – 0.72	<0.001
Kidney composite outcome	142 (6.6)	243 (11.3)	0.56	0.45 – 0.68	<0.001
Cardiovascular composite outcome	100 (4.6)	138 (6.4)	0.71	0.55 – 0.92	0.009
Death from any cause	101 (4.7)	146 (6.8)	0.69	0.53 – 0.88	0.004

CI – confidence interval; n (%) – number of patients with outcomes.

Table 5. Risk of outcomes for SGLT2 vs other GLDs group for patients with established CVD				
Outcome	SGLT2 N/year	Other GLDs N/year	Hazard ratio	95 % CI
Death	1.8	3.6	0.56	0.44 – 0.70
Heart Failure	2.3	3.2	0.72	0.63 – 0.82
Heart Failure or Death	4.0	6.7	0.63	0.57 – 0.70

CI – confidence interval; GLD - glucose-lowering drug; N/year – event rate per 100 patient-years.

Table 6. Risk of outcomes for SGLT2 vs other GLDs group for patients without established CVD				
Outcome	SGLT2 N/year	Other GLDs N/year	Hazard ratio	95 % CI
Death	0.5	0.9	0.56	0.50 – 0.63
Heart Failure	0.1	0.2	0.61	0.48 – 0.78
Heart Failure or Death	0.6	1.1	0.56	0.50 – 0.62

CI – confidence interval; GLD - glucose-lowering drug; N/year – event rate per 100 patient-years.

Researchers deduced that in type 2 diabetes patients who had or were at risk for atherosclerotic cardiovascular disease, treatment with dapagliflozin did not result in a higher or lower rate of MACE than placebo but did result in a lower rate of cardiovascular death or hospitalization for heart failure, a finding that reflects a lower rate of hospitalization for heart failure.

In Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure[6] the authors presented the result of a randomized, double-blind, parallel-group, placebo-controlled, event-driven trial. 3,730 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less received empagliflozin (10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of adjudicated cardiovascular death or hospitalization for heart failure, analyzed as the time to the first event. The first secondary outcome was an occurrence of all adjudicated hospitalizations for heart failure, including first and recurrent events. The second secondary outcome was the rate of the decline in the estimated glomerular filtration rate (GFR) during double-blind treatment.

The primary composite outcome of death from cardiovascular causes or hospitalization for heart failure occurred in 19.4% of patients in the empagliflozin group and 24.7% of patients in the placebo group. Empagliflozin also favorably influenced the two prespecified secondary outcomes. The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group (Table 3). The rate of the decline in the estimated GFR throughout the double-blind treatment period also was slower in the empagliflozin group than in the placebo group (–0.55 ml per minute per 1.73 m2 per year vs –2.28 ml per minute per 1.73 m2 per year). Uncomplicated genital tract infection was reported more frequently with empagliflozin.

The authors concluded that among patients receiving recommended therapy for heart failure, those in the empagliflozin group had a lower risk of cardiovascular death or hospitalization for heart failure than those in the placebo group, regardless of the presence or absence of diabetes.

In Dapagliflozin in Patients with Chronic Kidney Disease[7] the authors reported on the results of a randomized, double-blind, placebo-controlled, multicenter clinical trial. Researchers randomly assigned 4,304 participants with an estimated glomerular filtration rate (GFR) of 25 to 75 ml per minute per 1.73 m2 of the body-surface area and a urinary albumin-to-creatinine ratio (with albumin measured in milligrams and creatinine measured in grams) of 200 to 5,000 to receive dapagliflozin (10 mg once daily) or placebo. The primary composite outcome was the first occurrence of any of the following: a decline of at least 50% in the estimated GFR, the onset of end-stage kidney disease, or death from renal or cardiovascular causes. Secondary outcomes were, in hierarchical order, the composite kidney outcome of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal causes; a composite cardiovascular outcome defined as hospitalization for heart failure or death from cardiovascular causes; and death from any cause.
The primary composite outcome occurred in 197 participants (9.2%) in the dapagliflozin group and 312 participants (14.5%) in the placebo group. The incidence of each secondary outcome was lower in the dapagliflozin group than in the placebo group (Table 4).

The authors inferred that among patients with chronic kidney disease the risk of a composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal or cardiovascular causes was significantly lower with dapagliflozin than with placebo.

In Inhibitors and Cardiovascular Risk. An Analysis of CVD-REAL[8] the authors presented the results of the CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT2 Inhibitors) study. This study was a multinational, observational study in which adults with type 2 diabetes were identified. Patients prescribed an SGLT2, or other glucose-lowering drugs (GLDs) were matched based on a propensity score for initiation of an SGLT2. After propensity score matching, 306,156 patients were included in the analysis (153,078 patients in each treatment group). Baseline characteristics were balanced between treatment groups in patients with and without established cardiovascular disease (CVD). Hazard ratios (HRs) for the risk of death, HF (heart failure), and HF or death in patients with and without established CVD were estimated for each country and pooled.

At baseline, 13% of patients had established CVD. Compared with therapy using other GLDs, initiation of an SGLT2 was associated with a lower risk of death in patients with and without CVD. Researchers observed also associations between SGLT2 and lower risk of HF and the composite of HF or death in patients with and without established CVD (Table 5 and Table 6).

The authors concluded that initiation of SGLT2 was associated with a lower risk of death and HF regardless of pre-existing CVD.

In Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction[9] authors presented results of

DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial. In this phase 3, placebo-controlled trial, researchers randomly assigned 4,744 patients with New York Heart Association class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either dapagliflozin (at a dose of 10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of worsening heart failure or death from cardiovascular causes. An episode of worsening heart failure was either an unplanned hospitalization or an urgent visit resulting in intravenous therapy for heart failure. A key secondary outcome was a composite of hospitalization for heart failure or cardiovascular death. The additional secondary outcomes were the total number of hospitalizations for heart failure (including repeat admissions) and cardiovascular deaths; the change from baseline to 8 months in the total symptom score on the Kansas City Cardiomyopathy Questionnaire (KCCQ); a composite of worsening renal function, which was defined as a sustained decline in the eGFR of 50% or greater, end-stage renal disease or renal death; and death from any cause.

The results of DAPA-HF trial showed that event rates for all three components of the primary composite outcome favored dapagliflozin; the largest number of events of worsening heart failure were hospitalizations. Of the patients receiving dapagliflozin, 231 (9.7%) were hospitalized for heart failure, as compared with 318 patients (13.4%) receiving placebo. Death from cardiovascular causes occurred in 227 patients (9.6%) who received dapagliflozin and 273 (11.5%) who received placebo. The incidences of the secondary outcomes were also lower in the dapagliflozin group than in the placebo group (Table 7).

The authors gathered that among patients with heart failure and a reduced ejection fraction, the risk of worsening heart failure or death from cardiovascular causes was lower among those who received dapagliflozin than among those who received placebo, regardless of the presence or absence of diabetes.

In Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes[10] the authors reported on the results of Canagliflozin Cardiovascular Assessment Study (CANVAS) Program, which integrated data from two trials involving a total of 10,142 participants with type 2 diabetes and high cardiovascular risk. All potential participants completed a 2-week, single-blind, placebo run-in period. Participants in each trial were randomly assigned to receive canagliflozin or placebo and were followed for a mean of 188.2 weeks. The primary outcome was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. Sec-

Table 7. Risk of outcomes for dapagliflozin vs placebo group

Outcome	Dapagliflozin n (%)	Placebo n (%)	Hazard ratio	95 % CI
Hospitalization or an urgent visit for heart failure (primary outcome)	237 (10.0)	326 (13.7)	0.70	0.59 – 0.83
Hospitalization for heart failure (primary outcome)	231 (9.7)	318 (13.4)	0.70	0.59 – 0.83
Urgent heart-failure visit (primary outcome)	10 (0.4)	23 (1.0)	0.43	0.20 – 0.90
Cardiovascular death (primary outcome)	227 (9.6)	273 (11.5)	0.82	0.69 – 0.98
Cardiovascular death or heart-failure hospitalization (secondary outcome)	382 (16.1)	495 (20.9)	0.75	0.65 – 0.85
Total number of hospitalizations for heart failure and cardiovascular deaths (secondary outcome)	567	742	0.75	0.65 – 0.88
Change in KCCQ total symptom score at 8 month (secondary outcome)	6.1 ± 18.6	3.3 ± 19.2	1.18	1.11 – 1.26
Worsening renal function (secondary outcome)	28 (1.2)	39 (1.6)	0.71	0.44 – 1.16
Death from any cause (secondary outcome)	276 (11.6)	329 (13.9)	0.83	0.71 – 0.97

CI – confidence interval; KCCQ - Kansas City Cardiomyopathy Questionnaire; n (%) – number of patients with outcomes.

Table 8. Risk of outcomes for canagliflozin vs placebo group

Outcome	Canagliflozin N/year	Placebo N/year	Hazard ratio	95 % CI
Death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke	26.9	31.5	0.86	0.75 – 0.97
Hospitalization for any cause	118.7	131.1	0.94	0.88 – 1.00
Hospitalization for heart failure	5.5	8.7	0.67	0.52 – 0.87
Death from cardiovascular causes or hospitalization for heart failure	16.3	20.8	0.78	0.67 – 0.91
Death from any cause	17.3	19.5	0.87	0.74 – 1.01
Progression of albuminuria	89.4	128.7	0.73	0.67 – 0.79
40% reduction in eGFR, renal-replacement therapy, or renal death	5.5	9.0	0.60	0.47 – 0.77

CI – confidence interval; eGFR – estimated glomerular filtration rate; N/year – number of participants with an event per 1000 patient-years.

ondary outcomes planned for sequential conditional hypothesis testing were death from any cause, death from cardiovascular causes, progression of albuminuria, and the composite of death from cardiovascular causes, and hospitalization for heart failure. Researchers reported that significantly fewer participants in the canagliflozin group than in the placebo group had a primary outcome event. Although, based on the prespecified hypothesis testing sequence, the renal outcomes are not viewed as statistically significant, the results showed a possible benefit of canagliflozin concerning the progression of albuminuria and the composite outcome of a sustained 40% reduction in the estimated glomerular filtration rate, the need for renal-replacement therapy, or death from renal causes (Table 8).

The authors concluded that patients treated with canagliflozin had a lower risk of cardiovascular events than those who received placebo but a greater risk of amputation, primarily at the level of the toe or metatarsal.

In Trends in diabetes medication use in Australia, Canada, England, and Scotland: a repeated cross-sectional analysis in primary care[11] the authors described the uptake of new classes of medication (SGLT2s and DPP4s) among patients with type 2 diabetes. Authors reported that some newer drugs, such as sodium-glucose cotransporter 2 inhibitors (SGLT2s) and glucagon-like peptide 1 (GLP1), decrease the risk of adverse cardiac and renal outcomes in patients at higher risk, while others, such as dipeptidyl peptidase-4 inhibitors (DPP4s), are not better than placebo. The presented analysis is based on data from 238,619 patients that were included by 2017 in 2017: 106,000 patients in Australia, 28,063 in Canada, 88,953 in England, and 15,603 in Scotland.

The results showed that SGLT2s were rarely prescribed in 2012, by 2017, between 10.1% and 15.3% of patients were on that class. DPP4 usage ranged between 19.1% and 27.6% in 2017. Researchers reported that the uptake of SGLT2s was most pronounced in younger patients. They also compared their results with existing literature – a study using US claims data similarly found higher rates of adoption in younger patients with a lower risk. Based on existing literature the authors reported that current guidelines recommended SGLT2s for patients at greater cardiovascular risk. Researchers emphasized that longer life expectancy for younger persons entails greater medication costs over time; this may be balanced by larger decreases in cardiovascular outcomes owing to a longer use.

The authors concluded that even though SGLT2s and GLP1s have been associated with better cardiovascular outcomes, lower mortality, and more favorable effects on patient weight than DPP4s, the latter were still used more frequently than SGLT2s or GLP1s.

In Different patterns of second-line treatment in type 2 diabetes after metformin monotherapy in Denmark, Finland, Norway, and Sweden (D360 Nordic)[12] the authors presented results of a multinational observational study, which was part of the D360 Nordic program, a large-scale diabetes investigation program which utilizes the unique features of full coverage nationwide healthcare registries and public healthcare systems covering more than 25 million inhabitants in all the Nordic countries, to include all type 2 diabetes (T2D) patients with filled GLD prescriptions. In this study, all T2D patients aged 18 years and above who filled a GLD prescription from the beginning of the year 2006 to the end of the year 2015 were included. Patients with a diagnosis of type 1 diabetes, gestational diabetes, or polycystic ovarian syndrome were excluded. Second-line treatment was defined as ≥6 months (two reiteration prescription cycles of 3 months) of metformin monotherapy (at any dose), followed by a filled prescription of a second GLD class such as DPP4, SGLT2, GLP1, sulphonylurea, insulin, or other GLD (glitazones, acarbose, and glinides). The index date was defined as the date of the first filled prescription of the second-line drug. In 2015, there was a total of 1,078,692 GLD-treated T2D patients in the four countries (Denmark 180,742; Finland 367,356; Norway 177,171; and Sweden 353,423). A total of 33,880 (3.1%) patients initiated second-line treatment, and this proportion was very similar throughout the countries. Researchers reported that the second-line treatment patterns of filled GLD prescriptions showed rapid changes during the observation period years 2006-2015 in Finland, Denmark, and Norway, whereas the uptake of the newer GLDs (DPP4, SGLT2, and GLP1) was slower in Sweden. In 2015, second-line treatment is initiated after about 5 years (4.7-5.0 years) in Norway, Finland, and Sweden but slightly shorter in Denmark (4.4 years). Newer GLDs were extensively used as second-line agents in three of the Nordic countries (Finland 92%, Norway 71%, and Denmark 70%), but was lower in Sweden (44%). The results of the study showed that DDP4 was the most commonly used second-line therapy in all countries (Table 9).

The authors deduced that despite comparable demography and healthcare systems in four neighboring countries, surprisingly large differences in second-line use of newer GLDs were found. With recent evidence of potential cardiovascular benefits with newer GLDs, such differences may have an important impact on cardiovascular outcomes.

In Long-term trends in the prescription of antidiabetic drugs: real-world evidence from the Diabetes Registry Tyrol 2012–2018[13] the authors described the results of a long-term, real-world study on prescription changes in the Diabetes Registry Tyrol (DRT). Researchers analyzed 10,875 patients from the DRT from 2012 to 2018. The results confirmed that since 2012 the number of metformin prescriptions increased, as well as gliptins, SGLT2, and

GLP1. In the same period, a strong decrease was observed in the number of sulfonylurea prescriptions (Table 10).

Researchers reported that more than half (55.6%) of the patients received a metformin-based combination therapy with at least one other antidiabetic drug. The most prevalent combination was metformin with gliptin (19.5%), followed by metformin in combination with insulin or an analog (17.1%). The third most prevalent antidiabetic combination was metformin with SGLT2 (9.7%). The authors emphasized that metformin in combination with SGLT2 showed the steepest increase (Table 11).

Table 9. Second-line treatment, the year 2015, for Denmark, Finland, Norway, and Sweden

Second-line treatment	Denmark n (%)	Finland n (%)	Norway n (%)	Sweden n (%)
DPP4	3555 (56.0)	8165 (89.5)	2763 (55.1)	4551 (34.0)
SGLT2	360 (5.7)	193 (2.1)	536 (10.7)	579 (4.3)
GLP1-	510 (8.0)	46 (0.5)	247 (4.9)	769 (5.7)
Sulphonylurea	1317 (20.8)	120 (1.3)	1121 (22.3)	4068 (30.4)
Insulin	597 (9.4)	510 (5.6)	328 (6.5)	2451 (18.3)
Other	4 (0.1)	89 (1.0)	24 (0.5)	977 (7.3)

n (%) – number of patients.

Table 10. Absolute and relative values of single class medication therapies in the treatment of type 2 diabetes mellitus in the Diabetes Registry Tyrol and change over time from 2012 to 2018

Single class medication	% of prescriptions in 2012	% of prescriptions in 2018	Total number of patients 2012-2018	Change from 2012 to 2018 p-value
Metformin	45.4	59	5583 (51.34%)	0.002
Gliptins	23.3	34.1	3067 (28.20%)	0.013
SGLT2	0.06	23.4	1270 (11.68%)	<0.001
Sulfonylurea	17.3	4.6	994 (9.14%)	<0.001

Table 11. Absolute and relative values of combination therapies in the treatment of type 2 diabetes mellitus in the Diabetes Registry Tyrol and change over time from 2012 to 2018

Metformin-based combination	% of prescriptions in 2012	% of prescriptions in 2018	Total number of patients 2012-2018	Change from 2012 to 2018 p-value
Metformin and gliptin	7.8	17.5	2115 (19.5%)	0.024
Metformin and (insulin/ analogs)	18.6	23.9	1858 (17.1%)	0.003
Metformin and SGLT2	0.3	15.8	1049 (9.7%)	<0.001

Table 12. The number of patients who received SGLT2 - adult population

Age group	18 – 39	40 – 59	60 – 79	80 – 99
Number of patients n (%)	22 (1.73%)	437 (34.41%)	753 (59.29%)	58 (4.57%)

Table 13. Percentage of cardiovascular events in SGLT2 and insulin groups – adult population

Age group	SGLT2	Insulin total	Insulin beginners
18-44	1/327 (0.31%)	20/8,298 (0.24%)	6/3,423 (0.18%)
45-54	16/640 (2.50%)	69/4,071 (1.69%)	16/775 (2.06%)
55-64	51/1,685 (3.03%)	317/9,962 (3.18%)	60/1,513 (3.97%)
65-74	74/1,980 (3.74%)	1,008/18,112 (5.57%)	163/2,110 (7.73%)
75-84	45/603 (7.46%)	1,046/12,701 (8.24%)	168/1,312 (12.8%)
85+	9/97 (9.28%)	577/5,543 (10.41%)	95/635 (14.96%)
Total	196/5,332 (3.68%)	3,037/58,687 (5.17%)	508/9,768 (5.20%)

Table 14. Risk of cardiovascular events in SGLT2 and insulin total groups – adult population

SGLT2	Insulin total	RR	95 % CI
196/5,332 (3.68%)	3,037/58,687 (5.17%)	0.71	0.62 – 0.82

RR – relative rate; CI – confidence interval.

Table 15. Risk of cardiovascular events in SGLT2 and insulin beginners groups – adult population

SGLT2	Insulin beginners	RR	95 % CI
196/5,332 (3.68%)	508/9,768 (5.20%)	0.71	0.60 – 0.83

RR – relative rate; CI – confidence interval.

The results showed that patients aged 60–79 years received the most SGLT2 (59.29%) and patients aged 18 – 39 the least (1.73%) (Table 12).

The authors concluded that a significant increase was observed in SGLT2, metformin, gliptins, and GLP1 prescriptions. In contrast prescriptions for sulfonylureas declined significantly.

Real-world data from Poland

In a sample of 3.4 million inhabitants of Lesser Poland, we tried to detect the effects of SGLT2 use in Polish patients with diabetes. We compare SGLT2 group with insulin users, especially the cohort that started taking them at a similar time as gliflozin. Out of 5,332 patients (Table 13) who received reimbursed SGLT2 in the Lesser Poland National Health Fund in 2020, 196 were hospitalized due to cardiovascular incidents. It amounted to the complication rate of 3.68% and the percentage is lower than in patients treated with insulin - 5.17% (3,037/58,697), as well as in those who started insulin therapy in a similar period as patients treated with SGLT2 - 5.20% (508/9,768).

Patients treated with SGLT2 had a lower risk of cardiovascular events than those who received insulin (Table 14). The similar result was observed also for comparison of SGLT2 and insulin beginners (Table 15).

By comparing the obtained results of risk with the results from the publications discussed in the literature review we can see that our finds are similar to those from other research – in group of patients treated with SGLT2 the risk of cardiovascular event is lower than those who received insulin or other GLDs.

Analyzing the results for a group of patients aged 55 and over (Table 16) we can say that out of 4,365 patients aged 55 and over who received reimbursed SGLT2 in Lesser Poland Region in 2020, 179 were hospitalized due to cardiovascular incidents. The complication rate was equal to 4.10%. The percentage was lower by almost one-third than in patients treated with insulin - 6.36% (2,948/46,318). In those who started insulin treatment in a similar period as patients treated SGLT2 the complication rate was twice as high as for SGLT2 and amounted to 8.73% (486/5,570).

We can notice that in group of patients aged 55 and over treated with SGLT2 the risk of cardiovascular event is also significant lower than for patients who received insulin (Table 17).

The difference of risk of cardiovascular events in population aged 55 and over is also noteworthy for SGLT2 and insulin beginners groups (Table 18).

We also analyzed the number of patients treated with SGLT2 in age groups (Table 19).

The results showed that the patients aged 55 – 74 received the most SGLT2 (68,73%). Patients aged 18 – 44 and patients 85+ received the least. Our findings are similar to

Table 16. Percentage of cardiovascular events in SGLT2 and insulin – population aged 55 and over

Age group	SGLT2	Insulin total	Insulin beginners
55-64	51/1,685 (3.03%)	317/9,962 (3.18%)	60/1,513 (3.97%)
65-74	74/1,980 (3.74%)	1,008/18,112 (5.57%)	163/2,110 (7.73%)
75-84	45/603 (7.46%)	1,046/12,701 (8.24%)	168/1,312 (12.8%)
85+	9/97 (9.28%)	577/5,543 (10.41%)	95/635 (14.96%)
Total	179/4,365 (4.10%)	2,948/46,318 (6.36%)	486/5,570 (8.73%)

Table 17. Risk of cardiovascular events in SGLT2 and insulin total – population aged 55 and over

SGLT2	Insulin total	RR	95 % CI
179/4,365 (4.10%)	2,948/46,318 (6.36%)	0.64	0.55 – 0.74

RR – relative rate; CI – confidence interval.

Table 18. Risk of cardiovascular events in SGLT2 and insulin beginners – population aged 55 and over

SGLT2	Insulin beginners	RR	95 % CI
179/4,365 (4.10%)	486/5,570 (8.73%)	0.47	0.40 – 0.56

RR – relative rate; CI – confidence interval.

Table 19. Number of patients who received SGLT2 - adult population

Age group	18 – 44	45 – 54	55 – 64	65 – 74	75 – 84	85+
Total	327 (6.13%)	640 (12.00%)	1685 (31,60%)	1980 (37,13%)	603 (11,31%)	97 (1,82%)

Table 20. Percentage of cardiovascular events in SGLT2 group (adult population) by individual drugs

Age group	Canagliflozin	Dapagliflozin	Empagliflozin
Total	15/407 (3,69%)	30/1,173 (2,56%)	151/3,752 (4,02%)

those presented in Long-term trends in the prescription of antidiabetic drugs: real-world evidence from the Diabetes Registry Tyrol 2012–2018 (Table 12). In both research patients aged approximately 60 – 75 received the most SGLT2 and the patients aged 18 – 44 and 85+ received the least.

Data for individual reimbursed drugs from SGLT2 group were also studied, among which slight differences could be seen (Table 20). However, these data are not representative and should be treated with caution, due to the small research sample.

It should be noted that SGLT2 is also used by patients who buy them without reimbursement. Unfortunately, we are not able to obtain data on this group at the moment.

Conclusion

The clinical data suggest SGLT2 inhibitors' protection against cardiovascular outcomes and death. General improvement in cardiology-related health and descending hospitalization rates were observed in all clinical trials. A significant increase of SGLT2 prescriptions suggests this group of drugs became a substantial part of treatment across reporting countries.

No less important than the data from clinical trials is the information on the practical effectiveness of drugs, which comes from databases such as that on the National Health Fund. Among patients who took SGLT2, there was a lower percentage of hospitalizations due to cardiovascular events than in the insulin group. The same relationship occurred in the cohort of insulin users that started at a similar time as gliflozin. The data from the real practice confirms the thesis about the cardioprotective effect of SGLT2 inhibitors in Lesser Poland in one year horizon.
The reimbursement of SGLT2 in the limited population of diabetes patients was associated with some countable results. However, future studies for Poland based on real-world data are needed to assess the actual clinical results after the start of the use of gliflozin. Especially the longer follow-up and information from the National Health Fund databases covering the whole country should be provided.

Authors disclose no conflict of interest.

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