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**Prescribing Patterns of SGLT2 inhibitors and GLP**-**1 receptor agonists in Patients with T2DM and ASCVD in South Korea**

**Running title:** Use of SGLT2i and GLP1RA in T2DM and ASCVD

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**Abstract**

**Background:**

Despite cardiovascular benefits of sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP1RA) in patients with type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular disease (ASCVD), their utilization remains low globally. This study aimed to evaluate the utilization of SGLT2i and GLP1RA in patients with T2DM and ASCVD, as well as the factors associated with medications in South Korea.

**Methods:**

This retrospective study was conducted from 2015 to 2020, using National Patient Sample claims data. The study population included adult patients with confirmed T2DM and ASCVD diagnosed between March 1 and October 31 each year. Demographic and clinical characteristics, and influencing factors were investigated.

**Results:**

Among 57,576 study participants, SGLT2i use increased from 1.2 % to 10.51 % during the study period, whereas GLP1RA use increased slightly from 0 % to 1.17 %. Older age, comorbid chronic kidney disease, concurrent use of dipeptidyl peptidase 4 inhibitors (DPP4i), and prescriptions from specific physician specialties negatively influenced SGLT2i use. Conversely, comorbid dyslipidemia, heart failure, concurrent use of sulfonylurea (SU), and prescriptions from cardiologists positively influenced SGLT2i use. For GLP1RA, older age, concurrent DPP4i use, and specific physician specialty were negative factors, whereas female sex, dyslipidemia, insulin, and SU use were positive factors.

**Conclusions:**

Despite increasing utilization, 88.35 % of eligible patients remained untreated with SGLT2i and GLP1RA as of 2020. This study highlights the disparities in utilization based on patient characteristics and physician specialties, emphasizing the need to remove barriers and enhance clinical benefits for high-risk patients.

**Introduction**

Type 2 diabetes mellitus (T2DM) is a common chronic condition affecting millions of people worldwide1 and the prevalence of T2DM continues to increase. 2 T2DM is an important risk factor for atherosclerotic cardiovascular disease (ASCVD), making it imperative to effectively address its associated risks. 3,4 Particularly, individuals with both T2DM and ASCVD have higher risk for cardiovascular disease (CVD) and related mortality than those with T2DM alone, highlighting the importance of proactive CVD management and prevention in this particular population. 5

In recent years, several large clinical trials have been conducted to examine the cardiovascular risk reduction benefits of various antidiabetic agents. 6-12 Among these agents, sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP1RA) have demonstrated cardiovascular protective effects. 6-8,10-12 In individuals with T2DM, SGLT2i and GLP1RA have been shown to reduce major adverse cardiovascular events (MACE) by 11 % and 12 %, respectively. 13,14 Moreover, these agents have also demonstrated a substantial reduction in MACE, with a 14 % reduction for SGLT2i and a 13 % reduction for GLP1RA in individuals with concurrent ASCVD. 13,14 The accumulating evidence from these trials had led to a paradigm shift in the utilization of these agents. As a result, the updated guidelines of the American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), and Korean Diabetes Association (KDA) recommend the use of SGLT2i and GLP1RA in patients with T2DM and ASCVD to mitigate cardiovascular risk. 15-17

Despite these updated guidelines, global data have indicated insufficient utilization of SGLT2i and GLP1RA. 18-25 A nationwide study in the United States showed that the utilization rate of SGLT2i and GLP1RA increased between 2018 and 2021 in patients with T2DM and ASCVD; however, these agents remained underused in comparison with other antidiabetic agents, such as sulfonylureas (SU) and dipeptidyl-peptidase 4 inhibitors (DPP4i). 19 Similarly, a study conducted in the United Kingdom revealed an increase in the utilization rate of SGLT2i and GLP1RA in patients with T2DM and CVD; nevertheless, these agents were less commonly prescribed to patients with concomitant CVD than to those without CVD. 20 A Canadian regionwide study demonstrated increased use of SGLT2i and GLP1RA, but their utilization for cardioprotection still falls behind well-established secondary prevention agents like statins and angiotensin-converting enzyme inhibitors/angiotensin receptor antagonists (ACEi/ARB). 21

With the publication of several large clinical trials and changes in diabetes guidelines, considerable changes in prescription patterns and utilization of SGLT2i and GLP1RA for patients with T2DM and ASCVD were expected in South Korea. However, only a few studies have been conducted on this topic in South Korea. 26 Therefore, our study aimed to evaluate the yearly prescription trend for antidiabetic agents, including SGLT2i and GLP1RA, in patients with T2DM and ASCVD. In addition, we compared the characteristics of patients who received these medications with those who did not and examined the factors influencing their use.

**Methods**

***Data Sources***

We conducted a retrospective cross-sectional study from 2015 to 2020 using National Patient Sample data collected by the Korean Health Insurance Review and Assessment Service (HIRA-NPS). HIRA-NPS represents 2–3 % of claims data of the Korean population, with the proportion being 3 % prior to 2019. Because HIRA-NPS data are newly extracted every year, they do not contain continuous data across years.

The Korean health insurance system is categorized into three groups: National Health Insurance (NHI), Medical Aid (MedAid), and Patriots and Veterans Insurance (PVI). The majority of the Korean population are covered by NHI (97.2 %) and the remaining 3 % are covered by MedAid or PVI. 27

***Study Population***

Our study extracted data on adult patients aged ≥ 20 years with concurrent T2DM and ASCVD confirmed between March 1 and October 31 each year who were also prescribed at least one antidiabetic agent.

Initially, patients with T2DM were identified using the Korean Classification of Disease 7th edition (KCD-7) code E11, either as the main diagnosis or a sub-diagnosis. Patients aged < 20 years were excluded from the study. The presence of ASCVD was determined using both KCD-7 and procedure codes. ASCVD was defined in accordance with the guidelines of the American College of Cardiology and American Heart Association (ACC/AHA) 2013, encompassing ischemic heart diseases, such as myocardial infarction and angina, peripheral artery diseases, ischemic stroke, transient ischemic attack (TIA), and arterial revascularization procedures, including coronary interventions. 28 We evaluated all prescriptions within 60 days of the index date (the date when concurrent T2DM and ASCVD were initially identified), and included patients who were prescribed at least one antidiabetic agent as the final study population.

We collected demographic information for the study population, including age, sex, insurance type, region, type of medical institution, and physician’s specialty. Ages were stratified into 5 categories: 20–39, 40–49, 50–59, 60–69, and ≥70 years. Insurance types were divided into the NHI and MedAid/PVI groups. Medical institutions were grouped into five categories: tertiary hospitals, general hospitals, hospitals, clinics, and others. Regions were classified into three groups: capital city, metropolitan cities, and others. Physician specialties were categorized into five groups: cardiologists, endocrinologists, nephrologists, other internists (internists specializing in neither cardiology, endocrinology, nor nephrology), and other physicians.

Patients’ comorbidities were identified based on the identification of KCD-7 codes for additional diagnoses within 60 days preceding the index date. The use of other cardioprotective agents was determined based on prescriptions for statins or ACEi/ARB.

***Outcome***

The outcome of our study was the utilization of SGLT2i or GLP1RA after the identification of concurrent T2DM and ASCVD. Patients prescribed any of the following medications were considered SGLT2i users: dapagliflozin, empagliflozin, ipragliflozin, or ertugliflozin. Patients prescribed the following medications were classified as GLP1RA users: dulaglutide, exenatide, lixisenatide, or albiglutide. We identified factors influencing the prescription of these agents. Furthermore, we analyzed trends in the utilization of specific medication ingredients within the SGLT2i class. In cases where patients switched SGLT2i medications more than once within 60 days of the index date, the utilization rate of each medication was determined based on the initial SGLT2i prescription.

***Statistical analysis***

We analyzed the characteristics of the study population, comparing those prescribed SGLT2i and GLP1RA with those who were not, using percentages from frequency and the chi-square test for comparison. Multiple logistic regression analysis was used to assess the factors influencing the use of SGLT2i and GLP1RA. Additionally, we used the Cochran–Armitage trend test to confirm the significance of yearly utilization trends within the class of antidiabetic agents, including SGLT2i and GLP1RA.

We performed all analyses using the R Statistical Software (version 3.5.1; R Foundation for Statistical Computing, Vienna, Austria), and the level of significance was set at *p* < 0.05.

**Results**

***Characteristic of the Study Population***

Between 2015 and 2020, 57,576 patients with T2DM and ASCVD who were prescribed at least one antidiabetic agent were selected (Fig. 1). The utilization of SGLT2i increased more than 10-fold during study period, from 1.2 % in 2015 to 10.51 % in 2020 (Fig. 2). In contrast, the utilization rate of GLP1RA increased marginally from 0 % in 2015 to 1.17 % in 2020. By 2020, the proportion of patients treated with either of these agents reached 11.65 %.

In terms of the utilization of oral antidiabetic agents over the years, metformin consistently remained the most used drug. From 2015 to 2019, the top four oral antidiabetic agents used remained unchanged: metformin > DPP4i > SU > thiazolidinediones (TZD) (Fig. S1). However, in 2020, the utilization of SGLT2i (10.51 %) slightly surpassed that of TZD (10.15 %) (Table S1). Among non-cardioprotective antidiabetic agents, the use of DPP4i and TZD exhibited an increasing trend, whereas the use of SU showed a decreasing trend.

The overall utilization rate of SGLT2i was 5.84 % (n = 3365) (Table 1). The use of SGLT2i decreased with age, reaching the lowest value among those aged ≥ 70 years (2.76 %). Women had a lower utilization rate of SGLT2i compared to men. Regarding comorbidities, SGLT2i use was higher in patients with heart failure and dyslipidemia compared to those without these conditions. In contrast, patients with chronic kidney disease had lower SGLT2i utilization that those without. Patients prescribed other cardioprotective agents, such as statins and ACEi/ARB, had higher rates of SGLT2i use than those who were not prescribed these medications. Patients using DPP4i had significantly lower SGLT2i utilization compared to non-users (1.48 % vs. 11.87 %), whereas individuals using SU had higher utilization rates (6.19 % vs. 5.61 %). In terms of physician specialty, cardiologist had of the highest SGLT2i utilization (9.65 %), followed by endocrinologists, other internists, nephrologists, and other physicians.

The overall utilization rate of GLP1RA was 0.49 % (n = 284). GLP1RA utilization decreased with age. Patients with dyslipidemia or chronic kidney disease had higher GLP1RA utilization than those without these conditions. Patients treated with statins had higher GLP1RA use than those not treated with statins. Patients using DPP4i had a lower utilization rate of GLP1RA compared to non-users (0.12 % vs. 1.01 %), whereas those using SU had higher utilization rates compared to non-users (0.70 % vs. 0.35 %). Additionally, patients using insulin had significantly higher GLP1RA use compared to non-users (1.74 % vs. 0.33 %). Finally, endocrinologists had the highest GLP1RA use (1.01 %), followed by nephrologists, other internists, other physicians, and cardiologists.

***Factors Associated with the Use of SGLT2i and GLP1RA***

The results of the multiple logistic regression analysis are presented in Table 2. Advanced age was associated with reduced SGLT2i use. Among the comorbidities, heart failure and dyslipidemia had a positive influence on SGLT2i use. In contrast, chronic kidney disease was associated with the underutilization of SGLT2i. In terms of physician specialty, cardiologists were more likely to prescribe SGLT2i to patients with T2DM and ASCVD (OR = 1.22, [1.07, 1.40]) than were endocrinologists. In contrast, other internists and physicians were less likely to prescribe SGLT2i than were endocrinologists. Patients taking statins and ACEi/ARB were more likely to use SGLT2i than those not taking these medications. DPP4i use was a strong negative correlate SGLT2i use (OR = 0.09, [0.09, 0.10]), whereas SU use was associated with increased SGLT2i use (OR = 1.30, [1.20, 1.40]).

Regarding GLP1RA, patients > 50 years of age were less likely to use GLP1RA compared to those aged 20–30 years. Female patients were more likely to use GLP1RA (OR = 1.35, [1.06, 1.73]) than male patients. Comorbid dyslipidemia was a positive factor for GLP1RA use. Patients taking statins were more likely to use GLP1RA than those not taking statins. Notably, taking DPP4i emerged as a significant negative factor for GLP1RA use (OR = 0.12, [0.08, 0.16]). Conversely, SU and insulin use were independent strong positive factors associated with GLP1RA use (OR = 3.13, [2.44, 4.02] and OR = 3.71, [2.83, 4.85], respectively). Physicians specializing in cardiology, other internal medicine, and other specialties were less likely to prescribe GLP1RA in comparison to endocrinologists, with cardiologists being least likely to prescribe it (OR = 0.24, [0.10, 0.49]).

***Utilization trends for each SGLT2i agent***

Fig. 3 illustrates the proportion of each SGLT2i agent in relation to the total SGLT2i utilization per year. Dapagliflozin was dominant in 2015, accounting for 96.08 % of SGLT2i use (Table S2). The introduction of empagliflozin in South Korea in 2016 precipitated consistent upward trend in its share. Conversely, the share of dapagliflozin showed a consistent decline. In 2020, the combined use of dapagliflozin and empagliflozin accounted for more than 96 % of the total SGLT2i utilization.

**Discussion**

We observed a gradual increase in the utilization of SGLT2i and GLP1RA in patients with T2DM and ASCVD over the study period. From 2015 to 2020, the utilization rate of SGLT2i increased from 1.20 % to 10.51 %, whereas the usage rate of GLP1RA increased from 0 % to 1.17 %. Despite this growth, the utilization of SGLT2i and GLP1RA remained significantly lower than that of medications lacking evidence of cardioprotection, such as DPP4i and SU. Furthermore, the utilization rate of GLP1RA was notably lower than that of any other antidiabetic class.

We found that only 11.65 % of eligible patients taking SGLT2i and GLP1RA had received either of these agents by 2020. In contrast to previous studies conducted in the US and Australia, where over 20 % of patients with concurrent T2DM and ASCVD were using one of these agent, 19,29 it is evident that a substantial number of patients in South Korea did not receive adequate treatment. Furthermore, the utilization of SGLT2i and GLP1RA was significantly shorter than that of non-cardioprotective antidiabetic agents. Several previous studies have also shown that despite an increase in the utilization of SGLT2i and GLP1RA, non-cardioprotective antidiabetic agents were prescribed more frequently. 19,20,26 The underutilization of SGLT2i and GLP1RA could be attributed to clinical inertia. Despite the publication of various clinical trial results and updated guidelines, physicians tend to prescribe older medications over newer recommended options. 30,31 This tendency may be attributed to a lack of knowledge among physicians, reliance on their own clinical assessments, or consideration of patients preferences. 31,32 Moreover, the limited use of SGLT2i and GLP1RA could be linked to stringent insurance cover criteria. Specifically, SGLT2i were only covered by the NHI as an add-on therapy. Eligibility for SGLT2i cover required either intolerance to monotherapy or elevated HbA1C levels, which limited their accessibility. Similarly, GLP1RA required an add-on therapy status for insurance cover, with eligibility extended to patients with intolerance to dual oral agent therapy or insulin. For those intolerant to dual oral agents, additional criteria such as BMI ≥ or contraindication to insulin were required. The extremely low utilization of GLP1RA compared with that in other countries19,23-25 could be explained by these strict insurance cover requirements. Government efforts to lower the insurance cover threshold for SGLT2i and GLP1RA are needed to ensure adequate utilization of these agents.

We also identified factors influencing the use of SGTL2i and GLP1RA. Factors associated with low SGLT2i use included older age, the presence of comorbid chronic kidney disease, concurrent use of DPP4i and insulin, and receiving prescriptions from other internists and other physicians. Conversely, comorbid dyslipidemia and heart failure, concurrent use of statins and SU, and receiving prescriptions from cardiologists and endocrinologists were associated with high SGLT2i use. Regarding GLP1RA, factors associated with low GLP1RA use included older age, concurrent use of DPP4i, and receiving a prescription from other internists, other physicians, or cardiologists. Conversely, female sex, presence of dyslipidemia, and concurrent use of statins, insulin, and SU were associated with high GLP1RA utilization.

This study identified lower utilization rates of both SGLT2i and GLP1RA in older patients. This may be attributed to the concerns of physicians regarding complex comorbidities, polypharmacy, and adverse drug reactions (ADR) in this age group. 22,33 These concerns should be considered; nevertheless, it is essential to emphasize that older patients are more susceptible to cardiovascular diseases. 34 Thus, with closer monitoring and care, prescribing of SGLT2i and GLP1RA should be prioritized in older patients.

Notably, female patients were more likely to use GLP1RA (OR = 1.35, [1.06, 1.73]) than male patients. Weight management is particularly important in individuals with T2DM. 35 GLP1RA not only provide cardiovascular protection but also offers weight loss benefits. 36 Given that weight loss is more pronounced in women than men, 36,37 it is plausible that GLP1RA were prescribed more frequently for weight management in women and were their preferred choice. 38 There was no significant trend to use more SGLT2i for female patients, in contrast to the findings from previous studies. 21,25,39

The results also revealed a correlation between prescriptions and comorbidities. Patients with dyslipidemia were more likely to be prescribed both SGLT2i and GLP1RA than those without dyslipidemia. Given that elevated lipid levels are considered a risk factor for cardiovascular disease, 40 it is likely that physicians considered the lipid levels of these patients and prescribed SGLT2i and GLP1RA for their cardiovascular benefits. Patients with heart failure were more likely to be prescribed SGLT2i than those without heart failure. While a Canadian study identified concurrent heart failure as a negative factor (OR = 0.77, [0.74, 0.80]) for SGLT2i use in patients with T2DM and ASCVD, 21 our study revealed that SGLT2i were appropriately prescribed to patients with heart failure, consistent with the benefits of SGLT2i in heart failure. 41 In contrast, concurrent chronic kidney disease was negatively associated with SGLT2i use but did not affect GLP1RA utilization, despite both classes offering renal benefits. 13 As new indications and clinical evidence for SGLT2i and GLP1RA accumulate, it is essential for physicians to remain informed and assess patient comorbidities before prescribing.

Furthermore, our study identified that the use of DPP4i was significantly negatively associated with both SGLT2i and GLP1RA use (OR = 0.09, [0.09, 0.10] and OR = 0.12, [0.08, 0.16], respectively) in patients with T2DM and ASCVD. Combining DPP4i and GLP1RA is generally not recommended because these two classes of antidiabetic agents share a common mechanism of action, which revolves around enhancing the activity of the incretin hormone GLP-1 and no additional benefit has been identified when combined. 42 Therefore, this medication combination was not covered by NHI. In contrast, although combining SGLT2i with DPP4i may offer additional advantages, 43 such combination therapy was not covered by insurance. 26 This restriction might discourage dual therapies because of concerns about increased patient copayments. 44 Conversely, because combining SU with SGLT2i and GLP1RA were covered by insurance, the use of SU was associated with a higher utilization of both SGLT2i and GLP1RA. Similarly, patients using insulin were more likely to be prescribed GLP1RA. To ensure that appropriate and comprehensive treatments can be administered according to the patients’ clinical conditions, including their cardiovascular risk, government efforts are needed to expand insurance cover for antidiabetic agent combinations.

Moreover, differences in the utilization of SGLT2i and GLP1RA were observed based on the physician’s specialty. Cardiologists were more likely to prescribe SGLT2i than endocrinologists (OR = 1.22, [1.07, 1.40]). Previous studies in other countries have identified lower utilization of SGLT2i by cardiologists than by endocrinologists, along with their limited understanding of the cardiovascular benefits associated with SGLT2i. 21,45 However, our study demonstrated that cardiologists exhibited a better understanding of the cardiovascular benefits associated with SGLT2i. In contrast, GLP1RA were less likely to be prescribed by cardiologists than endocrinologists (OR = 0.24, [0.10, 0.49]). This could be attributed to patient and cardiologist preferences for oral medications over injectables, 46,47 particularly considering that GLP1RA are only available in an injectable form. Moreover, other internists and physicians were less likely to prescribe both SGLT2i and GLP1RA. Given that this group was responsible for prescribing to more than 60 % of patients, there is a clear need to facilitate their prescription of SGLT2i and GLP1RA.

Regarding trends in SGLT2i use, dapagliflozin accounted for 96.08 % of total SGLT2i use in 2015. Following the introduction of empagliflozin in 2016, its market share exhibited a consistent upward trend, reaching 44.01 % of total SGLT2i use in 2020. This upward trend may have been driven by the publication of trials on empagliflozin and its cardiovascular benefits. 48 The increase between 2018 and 2020 was more gradual than that in previous years, possibly due to the impact of trials related to dapagliflozin published in 2019. 7,8 It might have also been influenced by the broader insurance cover of dapagliflozin in comparison to empagliflozin during the study period. As additional trials continue to demonstrate the cardioprotective effects of other SGLT2i agents and insurance cover expands, future studies will be necessary to examine changes in the utilization of different SGLT2i components among patients with T2DM and ASCVD.

Our study had some limitations. First, we used claims data collected primarily for reimbursement purposes. Owing to the nature of the data, inaccuracies in diagnostic information that differ from the actual information may have been present. Second, our data lacked clinical information such as plasma glucose level, HbA1C, or disease severity. Furthermore, we lacked socioeconomic data including income levels and education. Although we used disease codes (KCD-7) instead of clinical parameters to determine the patients’ conditions, the availability of clinical information would have contributed to a more precise assessment of the patients’ status and medication use. Similarly, we were unable to consider factors such as patient intolerance, contraindications, or ADR when assessing medication use. Third, GLP1RA with evidence of CVD benefits (liraglutide and semaglutide) were not included in this study because of the lack of insurance cover during the study period. Similar to GLP1RA, given the favorable shifts in the reimbursement and accessibility of both SGLT2i and GLP1RA, there is an increasing need for future research that considers these developments.

Nevertheless, our study provides several significant insights. We have reported recent trends of SGLT2i and GLP1RA in patients with concurrent T2DM and ASCVD. Moreover, we identified not only the characteristics of the patients but also the factors influencing the use of SGLT2i and GLP1RA.

**Conclusions**

In patients with T2DM and ASCVD, although the utilization of SGLT2i and GLP1RA increased continually during the study period, 88.35 % of patients did not receive these agents even in 2020. We identified disparities in the use of SGLT2i and GLP1RA according to patients’ characteristics and physician specialties. Further efforts to eliminate barriers to the use of these agents are needed to enhance their clinical benefits by improving access in high-risk patients.

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We used National Patient Sample data from the Korean Health Insurance Review and Assessment Service (HIRA-NPS) from 2015 to 2020 (S20230711004); however, the study was not related to the Health Insurance Review and Assessment Service or the Ministry of Health and Welfare.

**Author declarations**

Ethical Approval

The Institutional Review Board of Pusan National University approved this study (PNU IRB/2023\_133\_HR).

Consent to participate

Not applicable

Consent to publish

Not applicable

Competing interests

The authors declare no conflict of interest associated with the research, authorship, or publication of this article.

Authors' contributions

YRE and NKJ conceived and designed the study; YRE, HJ, and SEC performed the analysis; YE first drafted the manuscript; each author contributed to drafting the article and endorsed the final version for submission to publication.

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Data availability

HIRA-NPS data were used in this study and were not permitted to be shared. Raw data were obtained with permission from the Health Insurance Review and Assessment Service of Korea (<http://opendata.hira.or.kr>).

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**Figure Legends**

**Figure 1.** Selection of the study population.

\* Date when concurrent T2DM and ASCVD were initially identified; T2DM: Type 2 diabetes mellitus; ASCVD, atherosclerotic cardiovascular disease; NPS: National patient Sample data.

**Figure 2.** The utilization rate of SGLT2i and GLP1RA between 2015 and 2020.

The *p* values for the Cochran-Armitage trend test of SGLT2i use, GLP1RA use, and use of either of them was less than 0.001. SGLT2i (green); GLP1RA (red); SGLT2i or GLP1RA (blue). SGLT2i: sodium-glucose cotransporter 2 inhibitors; GLP1RA: glucagon-like peptide-1 receptor agonists.

**Figure 3.** Trends in utilization of each SGLT2i agent between 2015 and 2020

The *p* values for the Cochran-Armitage trend test of each individual SGLT2i ingredient use were less than 0.001 (except ipragliflozin; ipragliflozin: *p* = 0.463). Proportion of dapagliflozin (red); proportion of ipragliflozin (purple); proportion of empagliflozin (green); proportion of ertugliflozin (blue). SGLT2i: sodium-glucose cotransporter 2 inhibitors.

**Table 1.** Characteristics of the study population categorized based on the use of SGLT2i or GLP1RA.

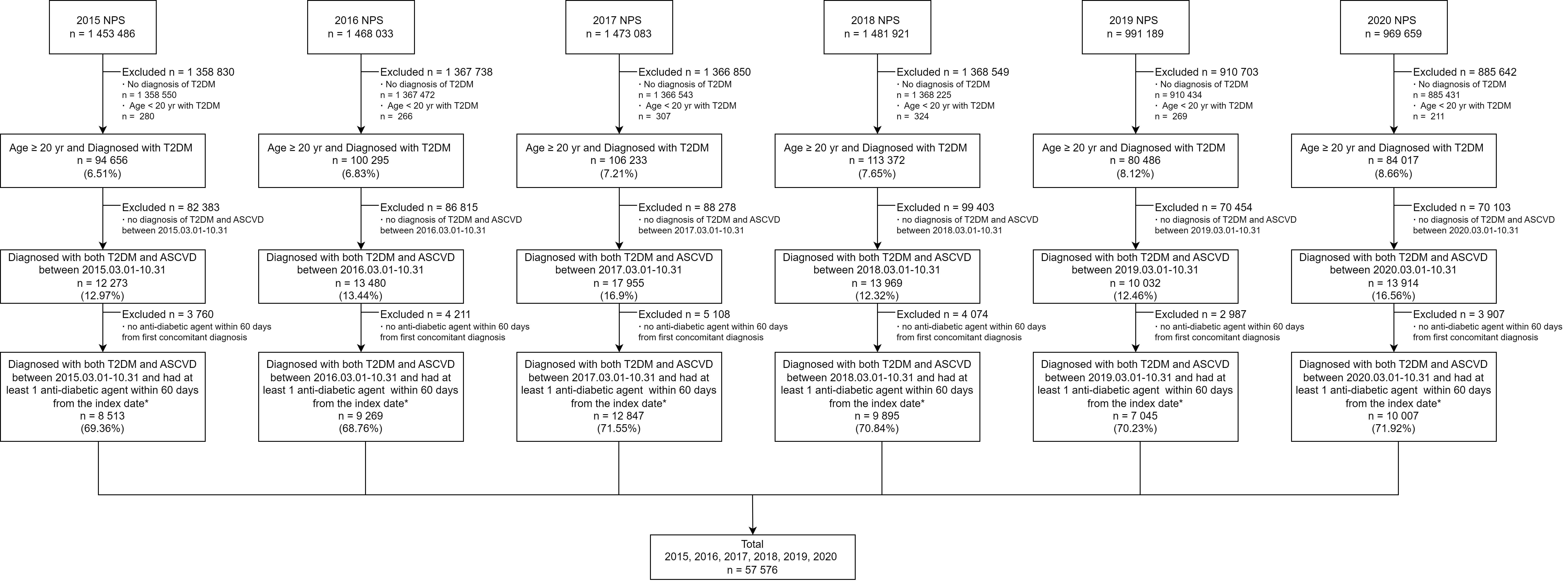
|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **SGLT2i** | |  | **GLP1RA** | |  | **SGLT2i or GLP1RA** | |  |
|  | ***N* (%)** | **Nonusers (%)** | **Users (%)** | ***p* value** | **Nonusers (%)** | **Users (%)** | ***p* value** | **Nonusers (%)** | **Users (%)** | ***p* value** |
| **Total** | 57 576 | 54 211 (94.16) | 3 365 (5.84) |  | 57 292 (99.51) | 284 (0.49) |  | 53 935 (93.68) | 3 641 (6.32) |  |
| **AGE** |  |  |  | < 0.001 |  |  | < 0.001 |  |  | < 0.001 |
| 20-39 | 635 (1.10) | 523 (82.36) | 112 (17.64) |  | 620 (97.64) | 15 (2.36) |  | 508 (80.00) | 127 (20.00) |  |
| 40-49 | 3 273 (5.69) | 2 851 (87.11) | 422 (12.89) |  | 3 229 (98.66) | 44 (1.34) |  | 2 809 (85.82) | 464 (14.18) |  |
| 50-59 | 11 316 (19.65) | 10 221 (90.32) | 1 095 (9.68) |  | 11 231 (99.25) | 85 (0.75) |  | 10 138 (89.59) | 1 178 (10.41) |  |
| 60-69 | 17 611 (30.59) | 16 558 (94.02) | 1 053 (5.98) |  | 17 528 (99.53) | 83 (0.47) |  | 16 477 (93.56) | 1 134 (6.44) |  |
| ≥70 | 24 741 (42.97) | 24 058 (97.24) | 683 (2.76) |  | 24 684 (99.77) | 57 (0.23) |  | 24 003 (97.02) | 738 (2.98) |  |
| **SEX** |  |  |  | < 0.001 |  |  | 0.700 |  |  | < 0.001 |
| Male | 30 861 (53.60) | 28 888 (93.61) | 1 973 (6.39) |  | 30 712 (99.52) | 149 (0.48) |  | 28 741 (93.13) | 2 120 (6.87) |  |
| Female | 26 715 (46.40) | 25 323 (94.79) | 1 392 (5.21) |  | 26 580 (99.50) | 135 (0.50) |  | 25 194 (94.31) | 1 521 (5.69) |  |
| **Institution** |  |  |  | < 0.001 |  |  | < 0.001 |  |  | < 0.001 |
| Tertiary | 9 854 (17.12) | 9 129 (92.64) | 725 (7.36) |  | 9 788 (99.33) | 66 (0.67) |  | 9 064 (91.98) | 790 (8.02) |  |
| General | 15 345 (26.65) | 14 337 (93.43) | 1 008 (6.57) |  | 15 240 (99.32) | 105 (0.68) |  | 14 234 (92.76) | 1 111 (7.24) |  |
| Hospital | 3 950 (6.86) | 3 760 (95.19) | 190 (4.81) |  | 3 934 (99.60) | 16 (0.40) |  | 3 746 (94.84) | 204 (5.17) |  |
| Clinic | 27 146 (47.15) | 25 732 (94.79) | 1 414 (5.21) |  | 27 049 (99.64) | 97 (0.36) |  | 25 638 (94.45) | 1 508 (5.55) |  |
| Others | 1 281 (2.22) | 1 253 (97.81) | 28 (2.19) |  | 1 281 (100) | 0 (0) |  | 1 253 (97.81) | 28 (2.19) |  |
| **Insurance** |  |  |  | 0.002 |  |  | 0.419 |  |  | 0.006 |
| NHI | 52 290 (90.82) | 49 183 (94.06) | 3 107 (5.94) |  | 52 036 (99.51) | 254 (0.49) |  | 48 937 (93.59) | 3 353 (6.41) |  |
| MedAid/PVI | 5 286 (9.18) | 5 028 (95.12) | 258 (4.88) |  | 5 256 (99.43) | 30 (0.57) |  | 4 998 (94.55) | 288 (5.45) |  |
| **Region** |  |  |  | 0.004 |  |  | < 0.001 |  |  | < 0.001 |
| Capital | 13 375 (23.23) | 12 536 (93.73) | 839 (6.27) |  | 13 282 (99.31) | 93 (0.69) |  | 12 445 (93.05) | 930 (6.95) |  |
| Metropolitans | 14 673 (25.49) | 13 782 (93.93) | 891 (6.07) |  | 14 606 (99.54) | 67 (0.46) |  | 13 717 (93.49) | 956 (6.51) |  |
| Others | 29 528 (51.28) | 27 893 (94.46) | 1 635 (5.54) |  | 29 404 (99.58) | 124 (0.42) |  | 27 773 (94.06) | 1 755 (5.94) |  |
| **Dyslipidemia** |  |  |  | < 0.001 |  |  | < 0.001 |  |  | < 0.001 |
| No | 11 789 (20.48) | 11 348 (96.26) | 441 (3.74) |  | 11 761 (99.76) | 28 (0.24) |  | 11 320 (96.02) | 469 (3.98) |  |
| Yes | 45 787 (79.52) | 42 863 (93.61) | 2 924 (6.39) |  | 45 531 (99.44) | 256 (0.56) |  | 42 615 (93.07) | 3 172 (6.93) |  |
| **Heart failure** |  |  |  | 0.012 |  |  | 0.299 |  |  | 0.007 |
| No | 50 432 (87.59) | 47 531 (94.25) | 2 901 (5.75) |  | 50 189 (99.52) | 243 (0.48) |  | 47 295 (93.78) | 3 137 (6.22) |  |
| Yes | 7 144 (12.41) | 6 680 (93.51) | 464 (6.49) |  | 7 103 (99.43) | 41 (0.57) |  | 6 640 (92.95) | 504 (7.05) |  |
| **CKD** |  |  |  | < 0.001 |  |  | 0.040 |  |  | < 0.001 |
| No | 54 490 (94.64) | 51 207 (93.98) | 3 283 (6.02) |  | 54 229 (99.52) | 261 (0.48) |  | 50 954 (93.51) | 3 536 (6.49) |  |
| Yes | 3 086 (5.36) | 3 004 (97.34) | 82 (2.66) |  | 3 063 (99.26) | 23 (0.74) |  | 2 981 (96.60) | 105 (3.40) |  |
| **Hypertension** |  |  |  | 0.128 |  |  | 0.427 |  |  | 0.076 |
| No | 14 438 (25.08) | 13 557 (93.90) | 881 (6.10) |  | 14 361 (99.47) | 77 (0.53) |  | 13 480 (93.37) | 958 (6.63) |  |
| Yes | 43 138 (74.92) | 40 654 (94.24) | 2 484 (5.76) |  | 42 931 (99.52) | 207 (0.48) |  | 40 455 (93.78) | 2 683 (6.22) |  |
| **ACEi/ARB** |  |  |  | 0.006 |  |  | 0.981 |  |  | 0.010 |
| No | 26 315 (45.71) | 24 854 (94.45) | 1 461 (5.55) |  | 26 185 (99.51) | 130 (0.49) |  | 24 726 (93.96) | 1 589 (6.04) |  |
| Yes | 31 261 (54.29) | 29 357 (93.91) | 1 904 (6.09) |  | 31 107 (99.51) | 154 (0.49) |  | 29 209 (93.44) | 2 052 (6.56) |  |
| **Statin** |  |  |  | < 0.001 |  |  | < 0.001 |  |  | < 0.001 |
| No | 21 130 (36.70) | 20 212 (95.66) | 918 (4.34) |  | 21 058 (96.66) | 72 (0.34) |  | 20 140 (95.32) | 990 (4.68) |  |
| Yes | 36 446 (63.30) | 33 999 (93.29) | 2 447 (6.71) |  | 36 234 (99.42) | 212 (0.58) |  | 33 795 (92.73) | 2 651 (7.27) |  |
| **DPP4i** |  |  |  | < 0.001 |  |  | < 0.001 |  |  | < 0.001 |
| No | 24 172 (41.98) | 21 302 (88.13) | 2 870 (11.87) |  | 23 928 (98.99) | 244 (1.01) |  | 21 065 (87.15) | 3 107 (12.85) |  |
| Yes | 33 404 (58.02) | 32 909 (98.52) | 495 (1.48) |  | 33 364 (99.88) | 40 (0.12) |  | 32 870 (98.40) | 534 (1.60) |  |
| **SU** |  |  |  | 0.004 |  |  | < 0.001 |  |  | < 0.001 |
| No | 34 111 (59.25) | 32 198 (94.39) | 1 913 (5.61) |  | 33 991 (99.65) | 120 (0.35) |  | 32 080 (94.05) | 2 031 (5.95) |  |
| Yes | 23 465 (40.75) | 22 013 (93.81) | 1 452 (6.19) |  | 23 301 (99.30) | 164 (0.70) |  | 21 855 (93.14) | 1 610 (6.86) |  |
| **Insulin** |  |  |  | 0.109 |  |  | < 0.001 |  |  | 0.006 |
| No | 50 976 (88.54) | 47 968 (94.10) | 3 008 (5.90) |  | 50 807 (99.67) | 169 (0.33) |  | 47 804 (93.78) | 3 172 (6.22) |  |
| Yes | 6 600 (11.46) | 6 243 (94.59) | 357 (5.41) |  | 6 485 (98.26) | 115 (1.74) |  | 6 131 (92.89) | 469 (1.11) |  |
| **Physician specialty** |  |  |  | < 0.001 |  |  | < 0.001 |  |  | < 0.001 |
| Cardiologists | 4 498 (7.81) | 4 064 (90.35) | 434 (9.65) |  | 4 491 (99.84) | 7 (0.16) |  | 4 057 (90.20) | 441 (9.80) |  |
| Endocrinologists | 13 213 (22.95) | 12 266 (92.83) | 947 (7.17) |  | 13 080 (98.99) | 133 (1.01) |  | 12 135 (91.84) | 1 078 (8.16) |  |
| Nephrologists | 1 287 (2.23) | 1 236 (96.04) | 51 (3.96) |  | 1 277 (99.22) | 10 (0.78) |  | 1 226 (95.26) | 61 (4.74) |  |
| Other internists | 25 009 (43.44) | 23 612 (94.41) | 1 397 (5.59) |  | 24 903 (99.58) | 106 (0.42) |  | 23 511 (94.01) | 1 498 (5.99) |  |
| Other physicians | 13 569 (23.57) | 13 033 (96.05) | 536 (3.95) |  | 13 541 (99.79) | 28 (0.21) |  | 13 006 (95.85) | 563 (4.15) |  |

SGLT2i, sodium-glucose cotransporter 2 inhibitors; GLP1RA: glucagon-like peptide-1 receptor agonists; NHI: National Health Insurance, MedAid: Medical Aid, PVI: Patriots and Veterans Insurance, CKD: chronic kidney disease; ACEi/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor antagonists; DPP4i, dipeptidyl-peptidase 4 inhibitors; SU: sulfonylureas.

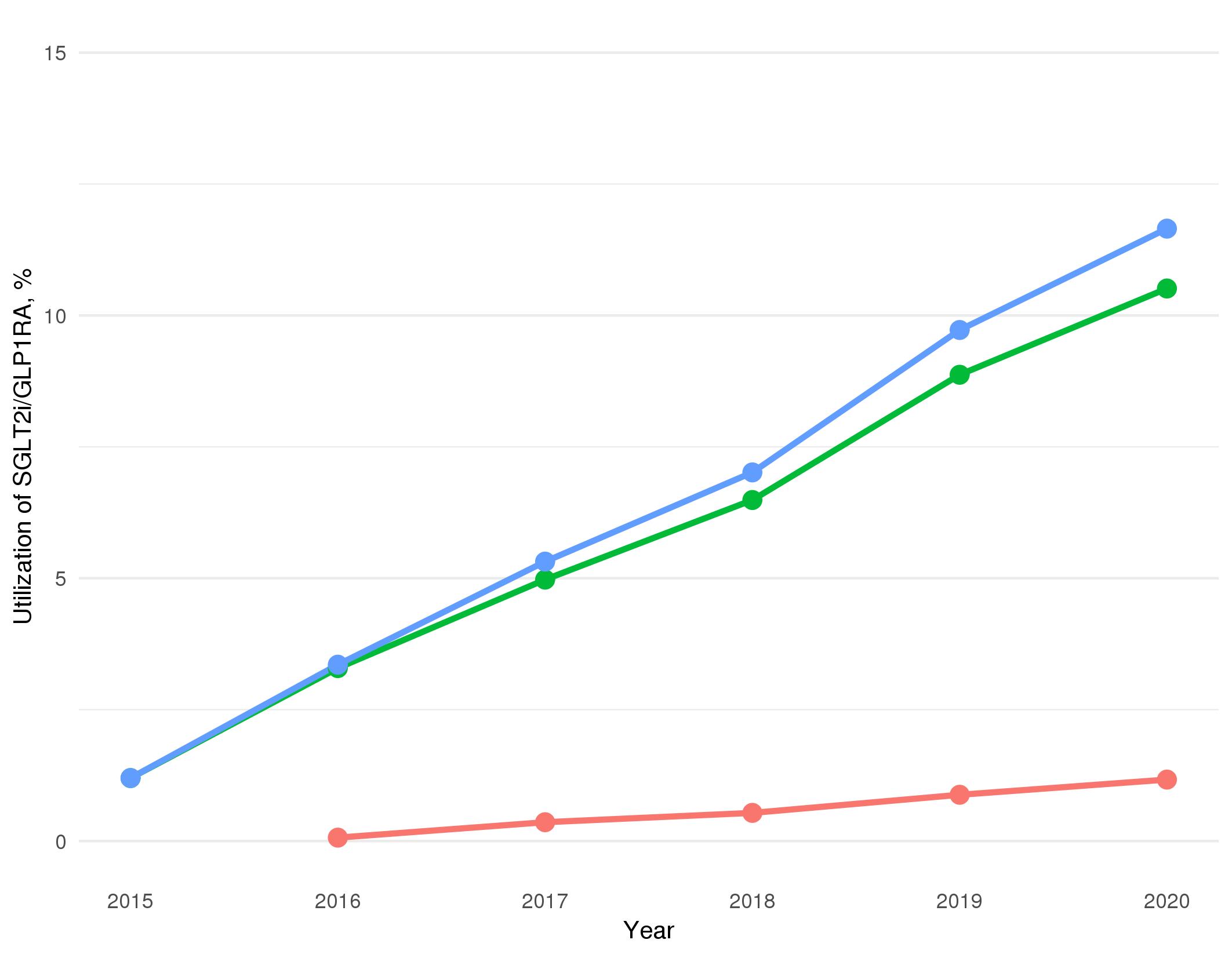
**Table 2.** Factors influencing the use of SGLT2i and GLP1RA

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **SGLT2i use** | | **GLP1RA use** | | **SGLT2i or GLP1RA use** | |
| **Adj. OR** | **97.5 % CI** | **Adj. OR** | **97.5 % CI** | **Adj. OR** | **97.5 % CI** |
| **AGE** |  |  |  |  |  |  |
| 20-30 (R) | 1 |  | 1 |  | 1 |  |
| 40-49 | 0.73 | 0.57-0.93 | 0.74 | 0.41-1.41 | 0.70 | 0.55-0.90 |
| 50-59 | 0.48 | 0.38-0.60 | 0.40 | 0.23-0.74 | 0.44 | 0.36-0.56 |
| 60-69 | 0.26 | 0.21-0.33 | 0.24 | 0.14-0.44 | 0.24 | 0.20-0.31 |
| ≥ 70 | 0.12 | 0.09-0.15 | 0.12 | 0.07-0.23 | 0.11 | 0.09-0.13 |
| **SEX** |  |  |  |  |  |  |
| Male (R) | 1 |  | 1 |  | 1 |  |
| Female | 1.02 | 0.95-1.10 | 1.35 | 1.06-1.73 | 1.05 | 0.97-1.13 |
| **Institution** |  |  |  |  |  |  |
| Tertiary (R) | 1 |  | 1 |  | 1 |  |
| General | 0.98 | 0.87-1.09 | 1.23 | 0.89-1.71 | 1.00 | 0.90-1.11 |
| Hospital | 0.88 | 0.71-1.08 | 1.35 | 0.66-2.7 | 0.90 | 0.73-1.11 |
| Clinic | 0.89 | 0.76-1.04 | 1.21 | 0.71-2.12 | 0.91 | 0.78-1.06 |
| Others | 0.51 | 0.33-0.76 | 0 | 0 | 0.50 | 0.32-0.74 |
| **Insurance** |  |  |  |  |  |  |
| NHI (R) | 1 |  | 1 |  | 1 |  |
| MedAid/PVI | 0.88 | 0.76-1.00 | 1.04 | 0.69-1.51 | 0.89 | 0.78-1.01 |
| **Region** |  |  |  |  |  |  |
| Capital (R) | 1 |  | 1 |  | 1 |  |
| Metropolitans | 1.04 | 0.94-1.16 | 0.80 | 0.57-1.11 | 1.02 | 0.92-1.13 |
| Others | 1.02 | 0.92-1.12 | 0.78 | 0.59-1.05 | 0.99 | 0.90-1.09 |
| **Dyslipidemia** |  |  |  |  |  |  |
| No (R) | 1 |  | 1 |  | 1 |  |
| Yes | 1.41 | 1.25-1.60 | 1.68 | 1.10-2.66 | 1.44 | 1.28-1.62 |
| **Heart failure** |  |  |  |  |  |  |
| No (R) | 1 |  | 1 |  | 1 |  |
| Yes | 1.22 | 1.09-1.37 | 1.32 | 0.92-1.85 | 1.24 | 1.11-1.38 |
| **CKD** |  |  |  |  |  |  |
| No (R) | 1 |  | 1 |  | 1 |  |
| Yes | 0.52 | 0.41-0.66 | 1.05 | 0.63-1.69 | 0.57 | 0.46-0.71 |
| **Hypertension** |  |  |  |  |  |  |
| No (R) | 1 |  | 1 |  | 1 |  |
| Yes | 0.96 | 0.87-1.07 | 0.94 | 0.67-1.32 | 0.95 | 0.86-1.06 |
| **ACEi/ARB** |  |  |  |  |  |  |
| No (R) | 1 |  | 1 |  | 1 |  |
| Yes | 1.13 | 1.03-1.24 | 1.02 | 0.76-1.39 | 1.13 | 1.03-1.23 |
| **Statin** |  |  |  |  |  |  |
| No (R) | 1 |  | 1 |  | 1 |  |
| Yes | 1.42 | 1.29-1.57 | 1.63 | 1.20-2.24 | 1.45 | 1.33-1.60 |
| **DPP4i** |  |  |  |  |  |  |
| No (R) | 1 |  | 1 |  | 1 |  |
| Yes | 0.09 | 0.09-0.10 | 0.12 | 0.08-0.16 | 0.09 | 0.08-0.10 |
| **SU** |  |  |  |  |  |  |
| No (R) | 1 |  | 1 |  | 1 |  |
| Yes | 1.30 | 1.20-1.40 | 3.13 | 2.44-4.02 | 1.41 | 1.31-1.51 |
| **Insulin** |  |  |  |  |  |  |
| No (R) | 1 |  | 1 |  | 1 |  |
| Yes | 0.63 | 0.56-0.71 | 3.71 | 2.83-4.85 | 0.80 | 0.71-0.90 |
| **Physician specialty** |  |  |  |  |  |  |
| Endocrinologists (R) | 1 |  | 1 |  | 1 |  |
| Cardiologists | 1.22 | 1.07-1.40 | 0.24 | 0.10-0.49 | 1.13 | 0.99-1.29 |
| Nephrologists | 0.85 | 0.61-1.15 | 0.80 | 0.37-1.58 | 0.84 | 0.62-1.12 |
| Other internists | 0.81 | 0.70-0.94 | 0.54 | 0.33-0.86 | 0.77 | 0.67-0.89 |
| Other physicians | 0.55 | 0.46-0.64 | 0.31 | 0.17-0.55 | 0.51 | 0.44-0.60 |
| **C statistic** | 0.821 |  | 0.880 |  | 0.823 |  |
| **p value of H-L test** | < 0.001 |  | 0.229 |  | < 0.001 |  |

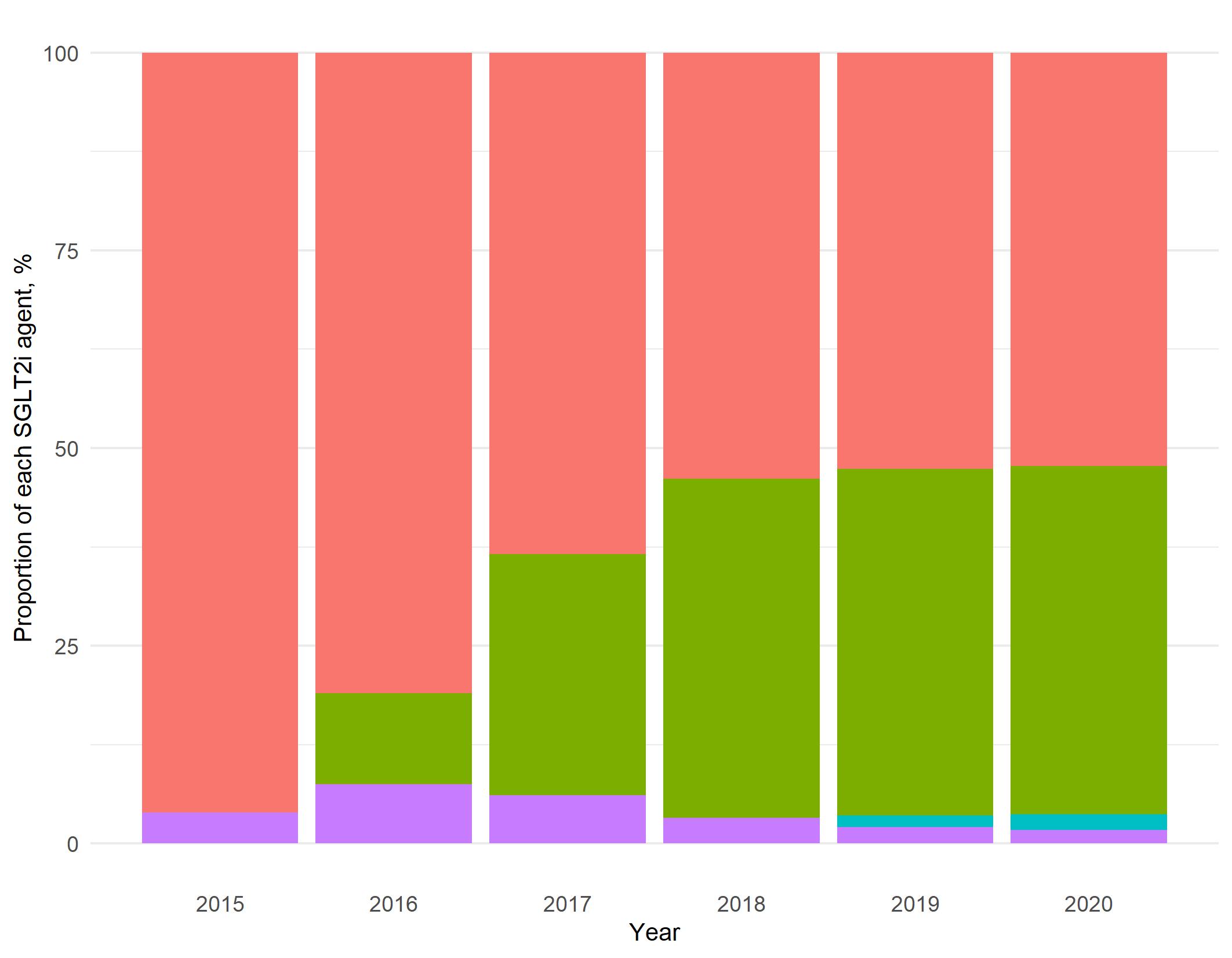
SGLT2i, sodium-glucose cotransporter 2 inhibitors; GLP1RA: glucagon- like peptide-1 receptor agonists; NHI: National Health Insurance, MedAid: Medical Aid, PVI: Patriots and Veterans Insurance, CKD: chronic kidney disease; ACEi/ARB, angiotensin-converting enzyme inhibitors/angiotensin receptor antagonists; DPP4i: dipeptidyl-peptidase 4 inhibitors; SU: sulfonylureas; H–L test: Hosmer–Lemeshow test.



**Figure 1.** Selection of the study population.



**Figure 2.** The utilization rate of SGLT2i and GLP1RA between 2015 and 2020.



**Figure 3.** Trends in utilization of each SGLT2i agent between 2015 and 2020