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Article

Assessment of the Utilization of Sodium–Glucose Cotransporter-2 Inhibitors in Patients Without Diabetes

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Abstract: Background: Sodium–glucose cotransporter-2 inhibitors (SGLT2Is) have demonstrated effects beyond glucose-lowering, leading to their approval for treating chronic heart failure (HF) in Japan. This study examines prescription trends for SGLT2Is in patients with diabetes versus those without diabetes, focusing on their backgrounds and HF treatment status of patients without diabetes who received SGLT2I after an HF diagnosis. Methods: Using data from DeSC Healthcare Inc., we analyzed patients aged 65 and above who received their first SGLT2I prescription between October 2014 and February 2023. Patients were classified into SGLT2I-treated diabetic and non-diabetic groups. We analyzed the annual prescription trends and compared the characteristics of both groups who started SGLT2I between 2022 and 2023. Additionally, we assessed the timing of SGLT2I initiation and the use of concomitant HF treatment in patients without diabetes after HF diagnosis. Results: The proportion of patients without diabetes receiving their first SGLT2I prescription has increased since 2021. Patients without diabetes receiving SGLT2Is were older, likely owing to aging-related diseases. In patients without a confirmed diabetes diagnosis, SGLT2I was most frequently initiated at the time of HF diagnosis. Mineralocorticoid receptor antagonists (MRAs) are the most common concomitant HF medications. The increase in SGLT2I prescriptions for patients without diabetes receiving SGLT2I since 2021, particularly in older individuals, suggests that SGLT2I is being initiated either at the time of HF diagnosis or in a stepwise manner. Conclusion: In Japan, MRA is commonly used as a concomitant medication in patients without diabetes receiving SGLT2I.

Keywords: sodium–glucose cotransporter 2; heart failure; diabetes; non-diabetes

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1. Introduction

Since sodium–glucose cotransporter-2 inhibitors (SGLT2Is) were first introduced as antidiabetic drugs in Japan in 2014, their use has increased significantly. According to a study using the National Database of Health Insurance Claims and Specific Health Checkups of Japan (NDB), dipeptidyl peptidase-4 inhibitors (DPP4Is) are the most prescribed diabetes treatment in Japan, followed by biguanides (BGs) and SGLT2Is [1,2]. This suggests that SGLT2Is, along with DPP4Is and BGs, are among the most frequently used diabetes medications.

Since 2015, randomized controlled trials (RCTs) have demonstrated effects beyond glycemic control for SGLT2Is [3,4]. In 2019, the effects of SGLT2 inhibitors on heart failure (HF) were demonstrated [5]; further, in 2020, their effects on HF were demonstrated regardless of the presence of diabetes [6]. The Japanese Circulation Society and the Japan Diabetes Society have also reported the effectiveness of SGLT2Is in preventing HF in patients with diabetes mellitus (DM) in a consensus statement [7]. Meta-analyses have further demonstrated their effectiveness in reducing the risk of cardiovascular events and improving kidney outcomes, highlighting their organ-protective effects [8].

The efficacy of SGLT2Is in treating HF has been demonstrated in patients with HF with reduced ejection fraction (HFrEF) [5,9] and in those with HF with preserved ejection fraction (HFpEF) [10,11]. Subsequently, international guidelines recommended the administration of SGLT2Is to patients with HF regardless of the presence of DM [12,13]. In Japan, dapagliflozin was approved for chronic HF in November 2020, followed by empagliflozin in November 2021 [14,15]. Additionally, according to the guidelines of the European Society of Cardiology, SGLT2Is are the only treatment strongly recommended for HFpEF [16]. Regarding the timing of SGLT2I initiation, an ongoing debate exists between the proposal for new sequencing, which advocates for the prompt introduction of SGLT2Is after HF diagnosis, and the conventional sequencing, which supports a more gradual introduction of SGLT2Is [17].

SGLT2Is are frequently used not only as antidiabetic agents but also as the most recommended treatment option for HF. In this context, an investigation into the administration of SGLT2Is in patients with HF abroad, stratified by the presence of DM, revealed a significant increase in the administration to patients with DM, whereas the increase in administration to patients without DM was not as pronounced. Gonzalez et al. suggested that the historical association of SGLT2Is with diabetes might cause hesitancy in prescribing them to patients without diabetes, even though such patients could benefit from SGLT2I therapy [18].

Currently, no consensus exists on the timing for initiating SGLT2I therapy in HF. Understanding how these medications are utilized as non-diabetic agents may help to reduce the number of undertreated patients. Therefore, this study aims to provide descriptive statistics on the prescription trends of SGLT2Is when administered as antidiabetic versus non-diabetic agents, along with insights into patient backgrounds. Additionally, we aimed to clarify the actual treatment policies regarding the use of SGLT2Is by describing the timing of SGLT2I initiation and their combination with other HF medications in patients without diabetes diagnosed with HF after SGLT2I administration, using health insurance claim data from three types of health insurers.

2. Results

2.1. Patient Background

As shown in Figure 1, according to the claim data, a total of 678,562 patients received at least one prescription of an SGLT2I from October 2014 to February 2023. Among them, 536,998 were elderly individuals aged 65 and over. Additionally, 294,405 patients had no SGLT2I administration for more than 6 months prior to the initial SGLT2I administration and had a confirmed diagnosis of DM, while 13,478 patients did not (Cohort 1). Between 2022 and 2023, the number of patients with and without diabetes receiving SGLT2Is was 91,587 and 10,280, respectively (Cohort 2). Of the 10,280 without diabetes, 8379 received SGLT2Is following an HF diagnosis (Cohort 3).

In Cohort 2, the mean age of patients with diabetes receiving SGLT2Is was 79.8 $\pm$ 7.2 years, while patients without diabetes had a significantly higher mean age of 82.4 $\pm$ 7.5 years. The prevalence of HF and the combination of HF medications, such as ARNI, MRA, low-ceiling diuretics, and high-ceiling diuretics, were significantly higher in patients without diabetes receiving SGLT2Is (Table 1).

2.2. Trends in SGLT2I Administration Rates Among Patients with and Without Diabetes Aged 65 and Older

In Cohort 1, the initial administration rate of SGLT2Is among patients without diabetes showed an uptrend, from 4.3% in 2021 to 13.6% by 2023 (Figure 2).

2.3. Duration from HF Diagnosis to SGLT2I Initiation Among Patients Without Diabetes

In Cohort 3, among patients without a confirmed diabetes diagnosis who received SGLT2Is after an HF diagnosis, 15.5% were initiated on SGLT2Is in the same month as their HF diagnosis. Subsequently, the SGLT2I initiation occurred 1 and 2 months later in 4.8%

and 2.1% of patients, respectively, with nearly consistent rates thereafter. Furthermore, 35.9% of patients began SGLT2I treatment within 12 months of their HF diagnosis (Figure 3).

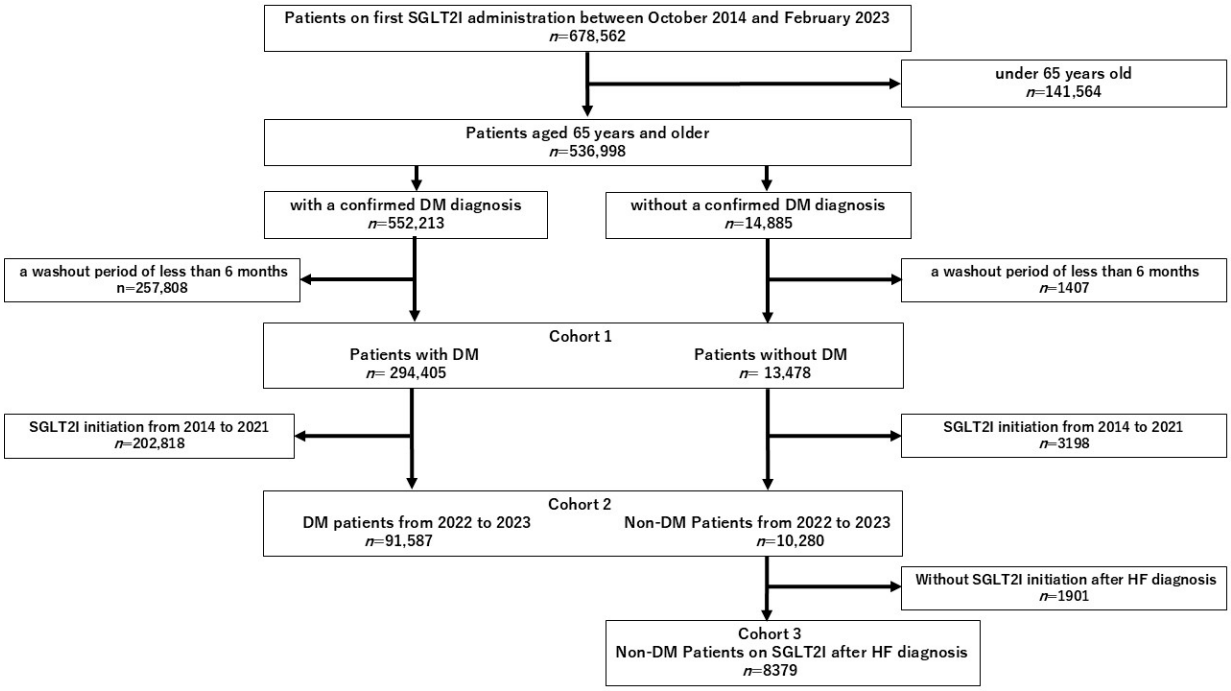

Figure 1. Flow chart showing the inclusion of patients. SGLT2I, sodium–glucose cotransporter-2 inhibitor; DM, diabetes mellitus; HF, heart failure.

Table 1. Baseline characteristics in Cohort 2.

	With DM n **= 91,587**	**Without DM** n **= 10,280**	p**-Value**
Demographic data and health insurance information			
Age (mean ± SD)	79.8 ± 7.2	82.4 ± 7.5	<0.01
Sex			
Male	52,264 (57.1%)	5425 (52.8%)	<0.01
Types of health insurance			
Health insurance	535 (0.6%)	39 (0.4%)	
National health insurance	21,215 (23.2%)	1445 (14.1%)	<0.01
Medical care system for the elderly in the latter stage of life	69,837 (76.3%)	8796 (85.6%)	
Drug			
ARNI	8522 (9.3%)	2082 (20.3%)	<0.01
β-blockers	14,808 (16.2%)	2383 (23.2%)	<0.01
Mineralocorticoid receptor antagonist	18,702 (20.4%)	4335 (42.2%)	<0.01
Low-ceiling diuretics	6030 (6.6%)	804 (7.8%)	<0.01
High-ceiling diuretics	22,496 (24.6%)	4695 (45.7%)	<0.01
ARB	48,342 (52.8%)	5453 (53.0%)	0.62
ACE inhibitors	8473 (9.3%)	1599 (15.6%)	<0.01
Digitalis preparations	2376 (2.6%)	518 (5.0%)	<0.01
Hyperpolarization-activated Cyclic Nucleotide-gated channel blocker	182 (0.2%)	55 (0.5%)	<0.01
Soluble guanylate cyclase stimulator	0 (0%)	0 (0%)	–
Disease			
Heart failure	45,987 (50.2%)	8216 (79.9%)	<0.01
Chronic kidney disease	16,027 (17.5%)	4280 (41.6%)	<0.01
Cardiovascular disease	13,038 (14.2%)	1306 (12.7%)	<0.01

DM, diabetes mellitus; SD, standard distribution; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor.

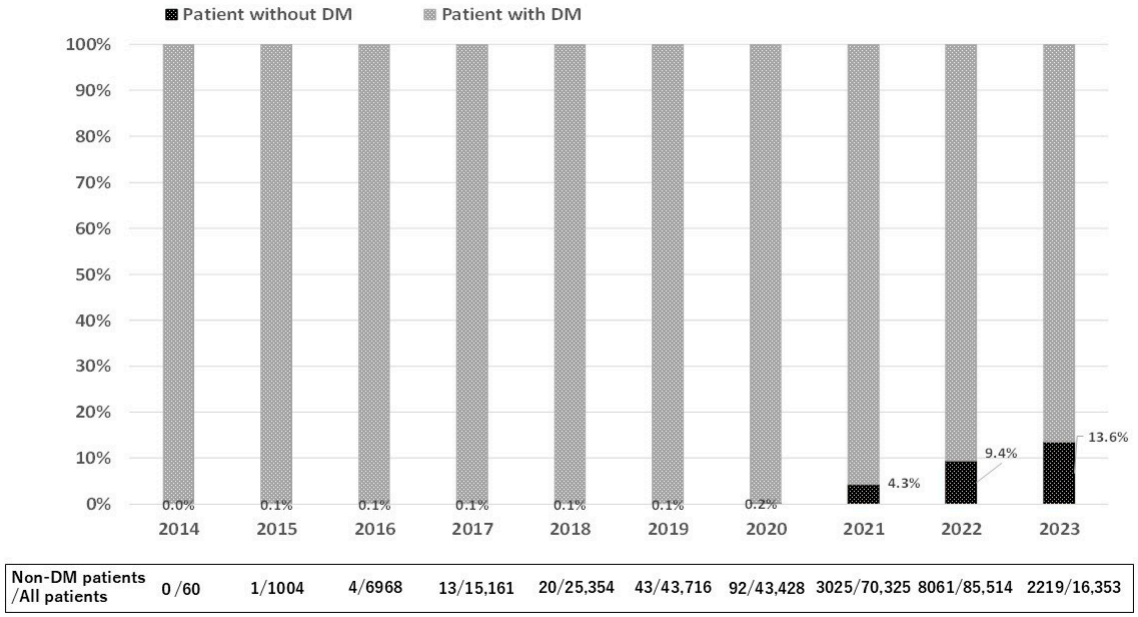

Figure 2. Proportion of sodium–glucose cotransporter-2 inhibitor administration between patients with and without diabetes. DM, diabetes mellitus.

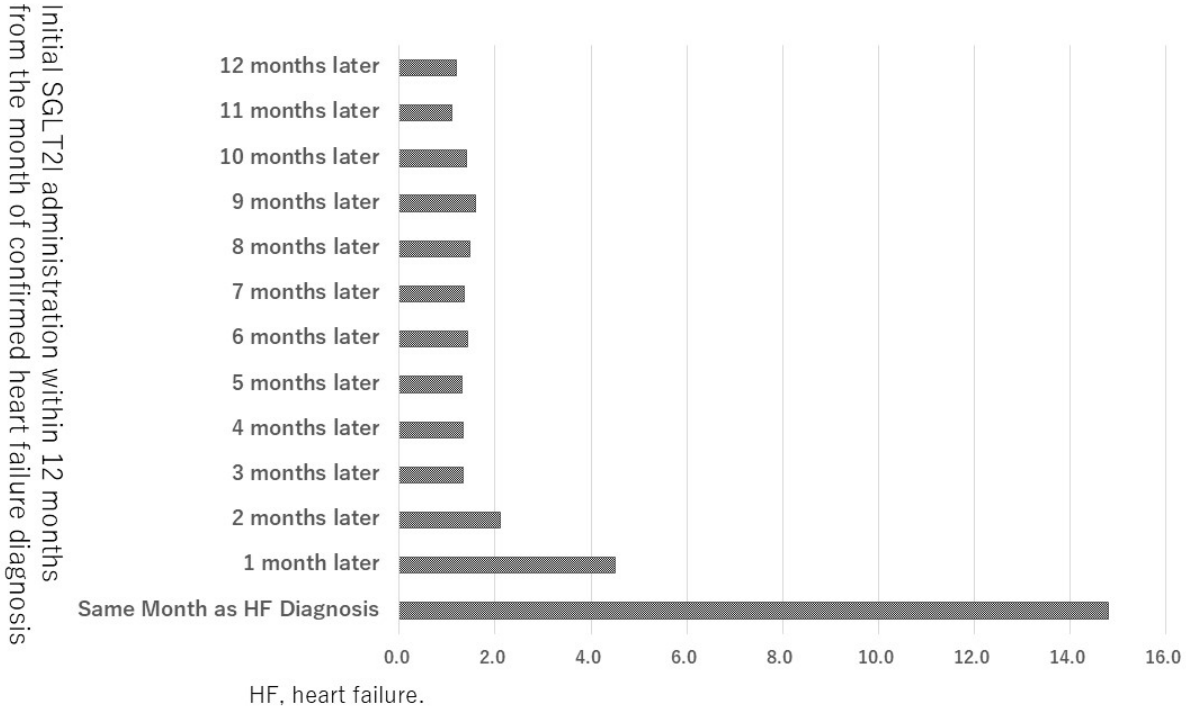

Figure 3. Period from the diagnosis date of heart failure to the initiation of sodium–glucose cotransporter-2 inhibitors. SGLT2I, sodium–glucose cotransporter-2 inhibitor.

2.4. Combination of Medications Related to HF Treatment at the Time of SGLT2I Initiation

In Cohort 3, the most common medication regimen involved one HF medication (40.2%), followed closely by SGLT2I monotherapy at 32.0%. Only 5.4% of patients received all recommended HF medications in combination (Table 2); when one medication was combined with an SGLT2I, MRAs were the most commonly prescribed. When two medications were combined, the combination of MRAs and β-blockers was most frequent (Table 3).

Table 2. Concomitant use of medications for heart failure treatment at the time of sodium–glucose cotransporter-2 inhibitor initiation.

	SGLT2I with HF ***n* = 8379**
Number of administered drug types *	
0	2683 (32.0%)
1	3364 (40.2%)
2	1884 (22.5%)
3	448 (5.4%)

SGLT2I, sodium–glucose cotransporter-2 inhibitor; HF, heart failure. * Drugs to be counted were angiotensin receptor–neprilysin inhibitors, beta-blockers, and aldosterone antagonists.

Table 3. Details and combinations of concomitant heart failure medications at sodium–glucose cotransporter-2 inhibitor initiation.

Drug Name or Drug Combination	**Count**
	3364
Mineralocorticoid receptor antagonist	2073
Beta-blockers	727
Angiotensin receptor–neprilysin inhibitor	564
	1884
Mineralocorticoid receptor antagonist and beta-blockers	871
Mineralocorticoid receptor antagonist and angiotensin receptor–neprilysin inhibitor	795
Beta-blockers and angiotensin receptor–neprilysin inhibitor	218

3. Discussion

The proportion of SGLT2Is administered as non-diabetic medications was significantly lower than the proportion administered as diabetic medications, but an increase was observed from 2021 onwards. Notably, the mean age of the patient cohort receiving SGLT2Is as non-diabetic medications was over 80 years, with a high prevalence of comorbidities, including HF and chronic kidney disease (CKD). Additionally, among patients without diabetes who received SGLT2Is after a diagnosis of HF, the timing of SGLT2I initiation was most frequently concurrent with the HF diagnosis. At the time of initiation, most patients frequently received a combination of MRA, ARNI, or β-blockers; however, some patients were also administered SGLT2Is as monotherapy.

The proportion of SGLT2I administration in patients without diabetes in this study was consistent with the prior research conducted by Gonzalez et al., which reported a rate of 12.3% in patients with HFrEF, suggesting no significant difference between the two studies [18]. The observed increase in SGLT2I administration rates is likely attributed to the expanded indications for HF treatment introduced in November 2020 [14,15]. In 2020, there were no changes in external factors, such as drug price adjustments, guideline revisions, or new research publications, which could have influenced SGLT2I usage trends, apart from the expanded indication. While the proportion of SGLT2Is administered as non-diabetic agents remains significantly low, Gonzalez et al. highlighted the potential for increased usage, noting that the historical association of SGLT2Is with diabetes may contribute to hesitancy in prescribing them as non-diabetic agents [18]. Therefore, it is anticipated that the use of SGLT2Is as non-diabetic agents will rise in Japan.

Regarding the use of SGLT2Is in patients with and without diabetes, the following patterns in prescribing practices were considered. With the expanded indication for HF, the use of SGLT2Is increased among diabetic patients with comorbid HF or CKD. Additionally, in patients without diabetes, the expanded indication for HF led to an increase in SGLT2I prescriptions for HF treatment. Therefore, we considered these two factors as the primary reasons for the increase in SGLT2I use. Regarding CKD, the Japanese Society of Nephrology recommends SGLT2Is for treating CKD regardless of the presence of diabetes [19]. The higher CKD comorbidity rate observed in this study compared to that reported by Gonzalez

et al. was likely influenced by the recommendation; similarly, the mean age of patients in this study was notably higher than that in Gonzalez et al.'s study (54.9 ± 8.9 years) [18]. Studies have reported that frailty and low BMI, common in the elderly, may lead to hesitancy in prescribing SGLT2Is [20], along with prior studies highlighting inadequate HF treatment [21]. Under such circumstances, patients without diabetes receiving SGLT2Is in Japan tend to be older and have a higher prevalence of comorbid CKD and HF. The prescription patterns of SGLT2Is in elderly patients were clarified, providing valuable insights for this population.

Regarding the timing of SGLT2Is, there is an ongoing discussion between the "Proposal New Sequencing", which advocates for prompt initiation following an HF diagnosis, and the "Conventional Sequencing", which supports a gradual approach to SGLT2I administration [17]. In this study, more than half of the patients had not initiated treatment within 1 year of the confirmed diagnosis. Additionally, 67.3% of patients were concurrently receiving either MRA, ARNI, or β-blockers at the time of SGLT2I initiation. These findings suggest that a stepwise approach to SGLT2I administration is commonly used in patient populations. However, since 15.5% of patients initiated SGLT2I treatment at the time of diagnosis, this suggests that both treatment approaches, immediate initiation and stepwise administration, are reflected in clinical practice. While MRA was the most commonly co-prescribed medication with SGLT2I in this study, β-blockers were more frequently used in overseas studies, indicating differences in combination therapy patterns. Both medications are considered first-line treatments [16], and this study demonstrated that MRA is the predominant co-prescribed drug among elderly patients without diabetes treated with SGLT2Is in Japan.

In terms of comorbidities, the presence or absence of cardiovascular disease has been suggested to influence HF treatment. Patients with cardiovascular disease are more likely to receive guideline-adherent pharmacotherapy [22]. In this study, the proportion of patients with cardiovascular disease was higher than the 8.0% reported by Gonzalez et al., making them more likely to receive SGLT2I therapy. However, the reported association between a history of cardiovascular disease and HF treatment remains debatable, and variations in definitions across studies warrant cautious interpretation.

The mean age of patients without diabetes administered SGLT2Is in this study was over 80 years. Although previous studies on SGLT2Is have focused on elderly patients, they did not distinguish between diabetic and non-diabetic medications [23–25]. Evans et al. noted that while the benefits of SGLT2Is beyond their glucose-lowering effects are clear, evidence specifically targeting the elderly population is lacking [26]. This study provides valuable insights into the characteristics of elderly patients without diabetes and current practices regarding SGLT2I and other HF treatments. Given the anticipated increase in SGLT2I prescriptions for patients without diabetes, continuous monitoring of patient demographics and prescribing practices is essential, along with exploring their potential as a first-line treatment for HF.

The limitations of this study include the reliance on disease definitions based solely on diagnosis codes and the inability to ascertain the severity of HF owing to the nature of the database research. Additionally, the database lacked detailed clinical information, limiting the ability to assess specific patient conditions or treatment responses. These factors may affect the generalizability of the findings and the interpretation of SGLT2I prescription patterns.

4. Materials and Methods

4.1. Database

This study used the DeSC Healthcare Inc. insurer database covering the period from April 2014 to August 2023. The DeSC Healthcare Corporation database (DeSC Data) includes health insurance claim data from three types of health insurers: (1) national health insurance, (2) health insurance, and (3) medical care system for the elderly in the latter stage of life, consisting of prescription and medical claims submitted monthly.

The national health insurance primarily covers self-employed individuals, while health insurance predominantly includes company employees and their dependents. The medical care system for the elderly in the latter stage of life covers a population of elderly individuals aged 75 and older. Therefore, the DeSC data encompasses a wide age range, from young adults to middle-aged and elderly individuals, with a higher proportion of individuals from the national health insurance compared to the overall population [27–29]. Given that it includes patients aged 75 years and older, the DeSC data are suited for studies primarily targeting older patients. In Japan, health insurance is broadly divided into three categories, each covering different age groups. The DeSC data used in this study include a higher proportion of elderly individuals compared to the proportion in the general population in Japan. Thus, taking advantage of this characteristic, we focused on investigating the situation among individuals aged 65 years and older. Several studies have been conducted in Japan using DeSC data [30,31].

The dataset included patient information from the insured ledger, such as sex, date of birth, and start date of data digitization for insurer data. It also contained disease-related information from medical receipts, including the International Statistical Classification of Diseases 10th Revision (ICD-10) master codes and disease codes from the receipt electronic processing system. Additionally, receipt information, which refers to insurance claim data compiled from itemized statements paid by insurers and contains coded information, including diagnosis names, prescribed medications with quantities, receipt IDs (unique codes assigned by DeSC Healthcare Inc. to each receipt), and subscriber IDs (unique codes assigned by DeSC Healthcare Inc. to each patient), was available. Pharmaceutical information, including Anatomical Therapeutic Chemical (ATC) classification codes and drug codes, was also obtained from the receipt electronic processing system.

This study used anonymized processed information derived from receipt data provided by DeSC Healthcare, Inc. Personal identifiers were removed, and a unique code was assigned to each dataset.

4.2. Definition of Patients with or Without Diabetes Administered SGLT2Is

From DeSC data, we extracted patients who had at least one prescription of SGLT2Is, indicated by the ATC code 'A10BK', between October 2014 and February 2023. We focused on patients aged 65 and older. In Japan, over half of diabetes patients are aged 60 years or older [32], and elderly diabetes patients are at a higher risk of renal dysfunction [33,34]. As the Guidelines for the Treatment of Elderly Diabetes define elderly patients as those aged 65 years or older, this study focused on individuals aged 65 years and above [35]. Among these individuals, patients with a confirmed diagnosis of diabetes classified under the ICD-10 codes E11 (Type 2 diabetes), E12 (diabetes related to nutritional disorders), E13 (other specified diabetes), or E14 (unspecified diabetes) were classified as SGLT2I-treated patients with diabetes, whereas the others were categorized as SGLT2I-treated patients without diabetes. Additionally, patients who had a period of more than 6 months prior to their initial SGLT2I administration were selected as the target population. First, to define a new prescription, we checked for any related prescriptions in the past 6 months. In Japan, there are no prescription duration restrictions; however, according to statistics from the Ministry of Health, Labour and Welfare, 97.9% of patients visit clinics within a 6-month interval [36]. Therefore, it was assumed that elderly patients with chronic conditions have at least one prescription record within this 6-month period. In Japan, there is a high prevalence of diabetes in elderly patients [32], and SGLT2Is are considered medications that require caution in recommendations [37]. Therefore, the study focused on elderly patients aged 65 and older (Cohort 1) (Figure 4).

SGLT2Is were approved for the additional indication of chronic HF in 2020 [14,15]. Given that prescribing trends may change following epidemiological events, such as the release of new drugs [38], the population of patients administered SGLT2Is might have differed. Therefore, we selected patients in the subgroup whose initial SGLT2I administration occurred in 2022 or 2023 (Cohort 2). Additionally, we formed a subgroup of

patients without diabetes administered SGLT2Is after a confirmed diagnosis of HF (I50) (Cohort 3). From DeSC data, we extracted patients who had at least one prescription of SGLT2Is, indicated by the ATC code 'A10BK', between October 2014 and February 2023. We focused on patients aged 65 and older.

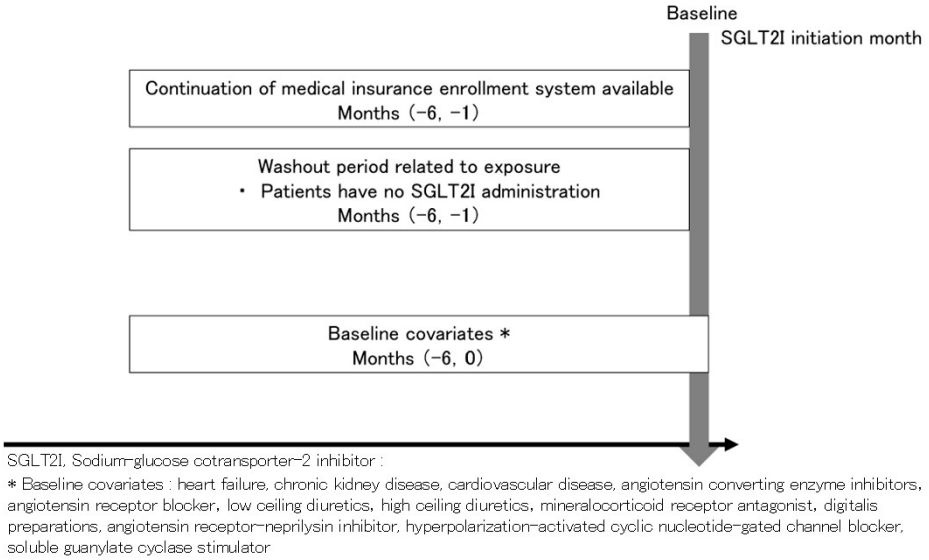

Figure 4. Definitions of each term in a diagram.

4.3. Definition of Concomitant Medications and Comorbidities

HF treatment includes various pharmacological agents. Given that the introduction of four medications—mineralocorticoid receptor antagonists (MRAs), angiotensin receptor–neprilysin inhibitors (ARNIs), β-blockers, and SGLT2Is—is recommended [39], we defined the criteria as having received any of these medications within 6 months prior to the initial administration of SGLT2Is based on ATC classification codes (Table S1). Other concomitant medications were defined as those received based on ATC classification codes within the same 6-month period, while comorbidities were defined as having a confirmed diagnosis of the relevant diseases based on ICD-10 codes within the 6 months prior to the month of initial SGLT2I administration [18,40–43].

4.4. Statistical Analysis

Statistical analyses were conducted using the statistical software SAS version 9.4. We compared the administration rates of SGLT2Is among patients with and without diabetes and the characteristics of both patient groups who received their initial SGLT2I administration between 2022 and 2023. We conducted descriptive statistics to analyze the time from a confirmed diagnosis of HF to the initiation of SGLT2Is in patients without diabetes, including the concomitant use of medications related to HF treatment and patient characteristics. Considering that SGLT2Is were first indicated for chronic HF in 2020, the time from a confirmed diagnosis of HF to the initiation of SGLT2I therapy was defined as within 12 months before SGLT2I administration. We conducted descriptive statistics using Cohorts 1–3. Cohort 1 was defined as the group of patients with diabetes and those without diabetes for analyzing trends in the use of SGLT2Is. Cohort 2 was defined as a subset of Cohort 1 comprising patients with and without diabetes who were prescribed SGLT2Is between 2022 and 2023. Given the increase in SGLT2I prescriptions since 2020, the study focused on the years 2022 and 2023. Cohort 3 was defined as a subset of Cohort 2 comprising patients who were diagnosed with HF prior to the prescription of SGLT2Is. Wilcoxon rank-sum and chi-square tests were used to analyze continuous and categorical variables, respectively. Statistical significance was set at a two-sided significance level of 5%.

4.5. Ethical Considerations

This was an observational study using de-identified and anonymized DeSC data, ensuring that patient names and the identities of the medical institutions providing the data were not linked. The data were processed on a secure, encrypted personal computer to ensure confidentiality. This study was approved by the Meiji Pharmaceutical University Research Ethics Committee (approval no. 202301).

5. Conclusions

SGLT2Is prescribed as non-diabetic medications are predominantly administered to elderly patients and may be initiated simultaneously with the diagnosis of HF or introduced in a stepwise manner. The use of combination medications for elderly patients receiving SGLT2I as a non-diabetic treatment in Japan is primarily centered around MRAs. However, there may be a latent population of patients who should be prescribed SGLT2Is as non-diabetic medications, highlighting the importance of closely monitoring future prescription trends. Future studies should explore the long-term outcomes of SGLT2I use in patients without diabetes, particularly in relation to HF progression and comorbidities. Additionally, further research is needed to assess the effectiveness of SGLT2I as a first-line treatment for elderly populations with diverse health profiles.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/pharma3040027/s1. Table S1: List of drugs and diagnoses with their corresponding codes.

Author Contributions: Conceptualization, T.K. and M.A.; methodology, T.K., M.Y. and M.A.; software, T.K., M.Y. and M.A.; validation, T.K. and M.A.; formal analysis, T.K. and M.A.; investigation, T.K., M.Y. and M.A.; resources, M.A.; data curation, M.A.; writing—original draft preparation, T.K. and M.A.; writing—review and editing, T.K. and M.A.; visualization, T.K. and M.A.; supervision, M.A.; project administration, M.A. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement: Not applicable.

Data Availability Statement: The data that support the findings of the study are available from the corresponding author upon reasonable request.

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Conflicts of Interest: Takuma Koinuma and Manato Yoshida have no conflicts of interest related to the publication of this paper. Manabu Akazawa has business outsourcing and advisory contracts with Astellas Pharma Inc., Janssen Pharmaceutical K.K., GlaxoSmithKline PLC., MSD, and Mitsubishi Tanabe Pharma Corporation, from which he received compensation.

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