Supplementary Materials

Cost-Effectiveness Analysis of SGLT2 Inhibitors for Cardio-Renal-Metabolic Disease Based on Data from Japanese Studies

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Appendix 1. Systematic literature review

1. Overview

The systematic literature review (SLR) was designed for both sensitivity and specificity, and was conducted according to the general recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [1], the general principles of the Centre for Reviews and Dissemination (CRD, University of York) guidance [2] for undertaking reviews in health care, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [3] and the general requirements of health technology assessment (HTA) agencies. The patient, intervention, comparator, outcome, and study design (PICOS) framework, data identification, data extraction, and quality assessment methods of SLR are presented in the sections below.

2. Eligibility criteria

The systematic literature search was performed using a pre-defined search strategy to identify eligible studies. The selection of studies for inclusion was determined using the PICOS framework [3]. The inclusion and exclusion criteria are presented in Table S1, Table S2, and Table S3.

Table S1. Eligibility criteria for incidence of complications

Category	Inclusion criteria	Exclusion criteria
Population	• Adult type 2 diabetes mellitus and non-type 2 diabetes mellitus population with cardiovascular or renal complications	• <18 years of age
Interventions /comparators	• N/A	• N/A
Outcomes	• Incidence/rates of chronic kidney disease/end-stage renal disease due to diabetic nephropathy in the diabetic population, and due to all causes • Incidence/rates of myocardial infarction/heart failure/stroke as diabetic complications in the diabetic population and due to all causes • Incidence/rates of myocardial infarction/heart failure/stroke events in the diabetic and non-diabetic populations	• Studies assessing outcomes not relevant to the review

Category	Inclusion criteria	Exclusion criteria
	• Incidence/rates of chronic kidney disease/end-stage renal disease in the diabetic and non-diabetic populations • All-cause mortality	
Study design	• Randomized controlled trial • Non-randomized controlled trial • Observational study • Case–control study • Cross-sectional, database, registry study • Cohort study or survey • Meta-analysis/systematic literature review	• Reviews, letters, comments, and editorials
Language	• English • Japanese	• Any other language
Countries	• Japan	• Any other country
Time limits	• Studies published from 2012 to 2022	• Studies before 2012

N/A, not applicable.

Table S2. Eligibility criteria for risk reduction

Category	Inclusion criteria	Exclusion criteria
Population	• Adult type 2 diabetes mellitus patients and non-type 2 diabetes mellitus patients	• <18 years of age • Animal study
Interventions /comparators	• Sodium–glucose cotransporter 2 inhibitors	• Intervention not mentioned in list
Outcomes	• Risk reduction in cardiovascular and kidney outcomes with sodium–glucose cotransporter 2 inhibitors • Risk reduction for cardiovascular disease onset in patients with non-type 2 diabetes mellitus plus chronic kidney disease • Risk reduction data for mortality	• Studies assessing outcomes not relevant to the review

Category	Inclusion criteria	Exclusion criteria
Study design	• Randomized controlled trial • Non-randomized controlled trial • Observational study • Case–control study • Cross-sectional study • Cohort study • Meta-analysis/systematic literature review	• Reviews, letters, comments, and editorials
Language	• English • Japanese	• Any other language
Countries	• Japan	• Any other country
Time limits	• Studies published from 2012 to 2022	• Studies before 2012

Table S3. Eligibility criteria for utility values

Category	Inclusion criteria	Exclusion criteria
Population	• Adult patients with myocardial infarction/heart failure/stroke or chronic kidney disease/end-stage renal disease	• <18 years of age • Population with any other disease from inclusion • Animal study
Interventions /comparators	• N/A	• N/A
Outcomes	• Utility values of myocardial infarction/heart failure/stroke or chronic kidney disease/end-stage renal disease	• Studies assessing outcomes not relevant to the review
Study design	• Randomized controlled trial • Non-randomized controlled trial • Observational study • Case–control study • Cross-sectional study • Cohort study • Meta-analysis/systematic literature review	• Reviews, letters, comments, and editorials

Category	Inclusion criteria	Exclusion criteria
Language	• English • Japanese	• Any other language
Countries	• Japan	• Any other country
Time limits	• No restrictions	• None

N/A, not applicable.

3. Search strategy

Search strategies were developed through the combination of free text words, indexing terms (e.g., medical subject headings [MeSH] terms for MEDLINE and Emtree terms for Embase), and using Boolean operators (e.g., 'and', 'or') on the terms relevant to disease area, interventions, and study designs. Outcome measures were not included in the search strategy but were incorporated into the inclusion/exclusion criteria of the SLR. The search strings were appropriately modified to fit each database-specific syntax.

4. Study selection process

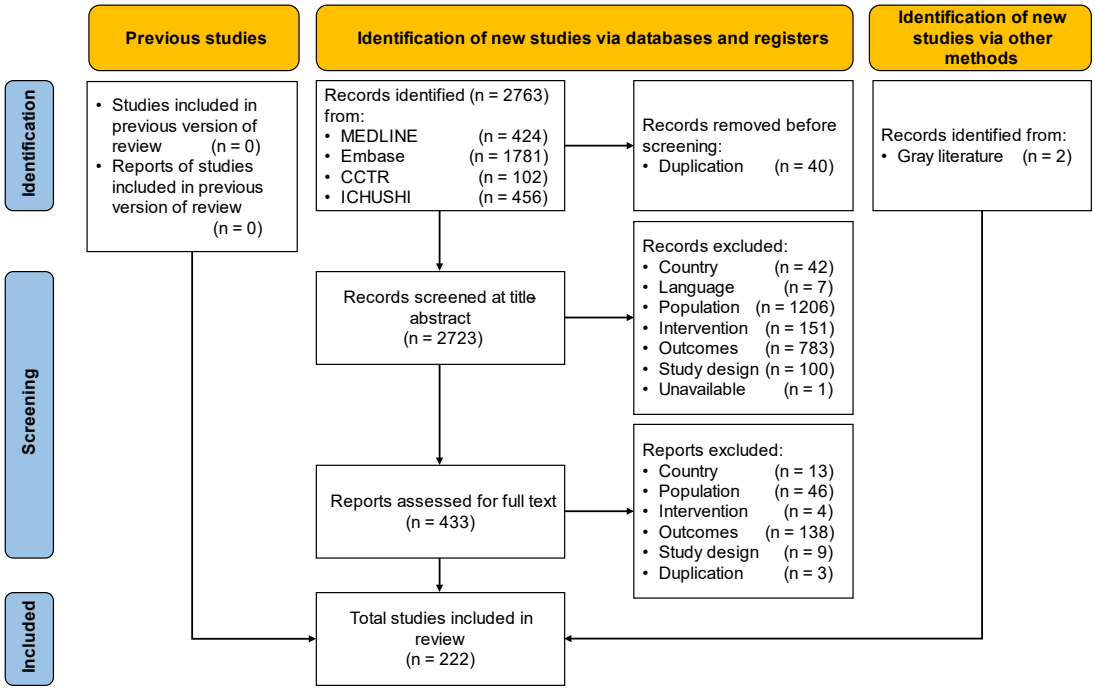
All retrieved studies were assessed against the eligibility criteria by two independent reviewers in both title/abstract and full-text review. For the abstract review, studies identified during the search were reviewed based on their abstracts and titles by two reviewers independently against pre-determined eligibility (inclusion/exclusion) criteria using the PICOS framework. Uncertainty or disagreement was resolved either through "reconciliation" (discussion between the two reviewers) or through "arbitration" by a third independent reviewer. For the full-text review, publications selected as potentially relevant from the abstract review were retained. Full-text publications were independently assessed by two reviewers and discrepancies were resolved by consulting a third independent reviewer. All papers included in the full-text review were retained for data extraction and quality appraisal. The PRISMA flow diagram is shown in Fig. S1.

5. Quality assessment

The quality of each study included in the SLR was assessed to ensure that the conclusions and findings of this review were based on the best available evidence and that any potential sources of bias in the data were identified. The quality of randomized controlled trials retained for data extraction was assessed in accordance with the NICE Single Technology Appraisal 2017 user guide [4], whereas the Newcastle–Ottawa Quality Assessment was used for case–control and cohort studies. The Joanna Briggs Institute critical appraisal checklist was used for quality assessment of cross-sectional studies. The NICE checklist is a globally accepted tool for assessing the publication quality of randomized

controlled trials [5]. The results of the validity assessment were not explicitly used in the analysis but served as additional information to determine the quality of the evidence base when interpreting the results.

Fig. S1. PRISMA flowchart



CCTR, Cochrane Central Register of Controlled Trials.

Appendix 2. *Ad hoc* analysis for SGLT2i effects

Risk ratios between sodium–glucose cotransporter 2 inhibitors (SGLT2i) and other glucose-lowering drugs (GLD) for the development of cardiovascular and renal complications in patients with type 2 diabetes mellitus (T2DM) were reported using Japanese real-world data. An *ad hoc* analysis of a previous study [6] was conducted as follows to exclude patients with potential off-label use of SGLT2i and other GLD.

A total of 313,862 patients with T2DM were allocated either SGLT2i (n=25,306) or other GLD (n=288,556) (Fig. S2). After propensity score (PS) matching, patient characteristics of each group were well balanced (Table S4), and hazard ratios for clinical events were calculated using pairs of 25,305 patients. Compared with other GLD, SGLT2i significantly reduced the risk of heart failure (HF), stroke, chronic kidney disease (CKD), and all-cause mortality, and numerically but not statistically reduced that of myocardial infarction (MI) (Table 2).

1. Data sources

The Medical Data Vision (MDV) database was used. The MDV database is a hospital-based database that contains administrative claims and laboratory data, and is linked to the Diagnostic Procedure Combination (flat-fee payment system) inpatient hospital payment system. The data period was from April 2008 to September 2018.

2. Analysis populations

The analysis population consisted of patients fulfilling the following criteria: >18 years of age on the index date, new users of any GLD (ATC code, A10) other than short-acting insulin (ATC code, A10AB) prior to the index date, without any history of cardiovascular (ICD-10 code, G45, I11.0, I13.0, I13.2, I20.0, I20.1, I20.8, I20.9, I21–I22, I25.1, I25.2, I25.5, I25.6, I48, I50, I60–I66, I70.2, I73.9, I74.2–9) and renal disease (ICD-10 code, N03, N05–N08, N17, N18–N19, E10.2, E11.2, E12.2, E13.2, E14.2, I12, I13.1, I13.2), without a history of gestational diabetes (ICD-10 code, O24.4), and without a history of type 1 diabetes (ICD-10 code, E10). A new user was defined as an individual receiving a prescription or filling a prescription of each separate diabetes medication class (SGLT-2i, metformin, sulfonylurea, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonist, glinides, glitazones, α-glucosidase inhibitor, insulins) with no issued/dispensed prescriptions of that medicine class during the preceding year. In addition, the analysis population consisted of patients with an on-label initial dose for each separate diabetes medication (GLD except for insulins). On-label/off-label could not be discriminated in insulin owing to a lack of information on the units needed for a particular patient.

3. Index date

The index date was defined as the date an individual met the new user criteria (as described above) regarding issued/filled prescription of the SGLT2i and other GLD classes during the study period. For the other GLD group, which comprised all diabetes medications except for SGLT2i, the first initiation of a new diabetes medication class was the index date for those initiating only one treatment episode in this group during the study period. For patients initiating two or more new diabetes medication classes during the study period, one of the treatment episodes for new diabetes medication classes was randomly selected and the first day of that episode was defined as the index date for that patient.

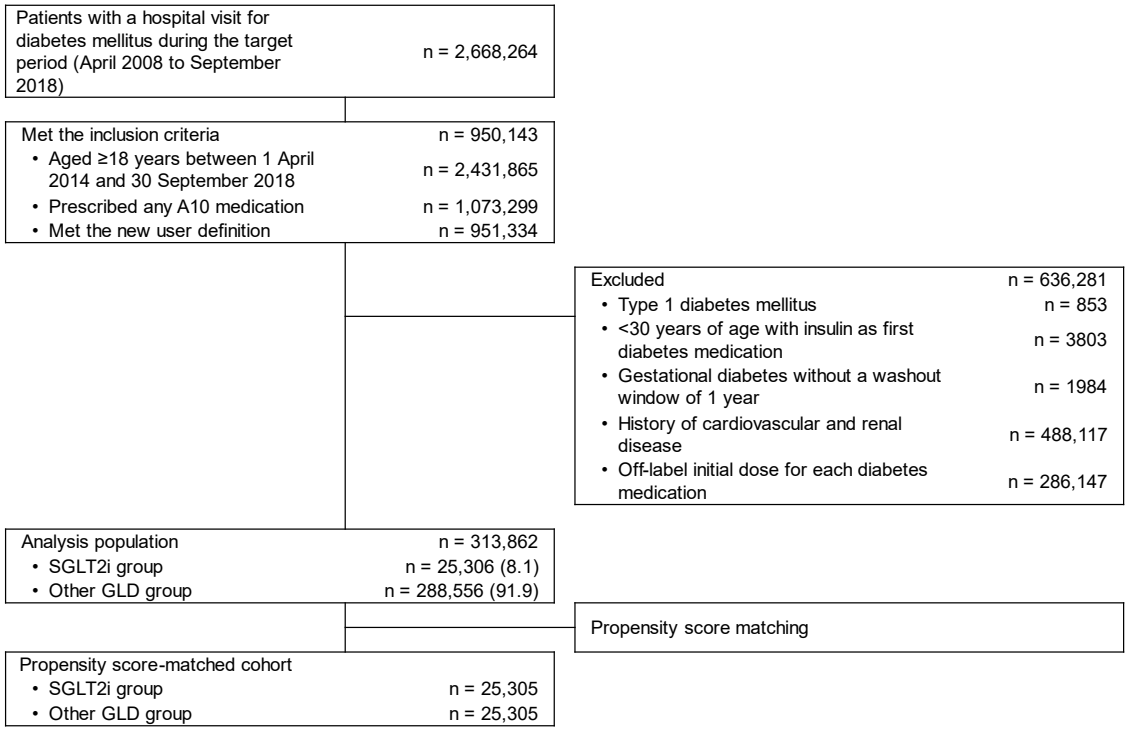
4. Outcome variables

Outcome variables were defined by corresponding ICD-10 codes described in Komuro et al. [6]. We assessed time to events for HF, MI, stroke, CKD, and all-cause mortality. Follow-up was continued even after patients discontinued their index treatment or switched to another treatment. The follow-up period was from the index date to the date of death, loss to follow-up (last hospital visit), or occurrence of a clinical event of interest, whichever occurred first.

5. Statistical analysis

The probability of having a new drug initiation of SGLT2i in each group was estimated using a logistic regression model to derive PS based on baseline demographics and clinical characteristics: age, sex, major organ-specific bleeding, cancer, CKD, dialysis, bariatric surgery, microvascular complications, severe hypoglycemia, lower limb amputations, chronic obstructive pulmonary disease, angiotensin II receptor blockers or angiotensin-converting enzyme inhibitor treatment, beta-blockers, high-ceiling diuretics, aldosterone, warfarin, digitoxin/digoxin, flecainide, amiodarone, statins, low-dose acetylsalicylic acid, receptor P2Y12 antagonists, direct factor Xa inhibitor (novel oral anti-coagulants), other antiplatelets, dihydropyridines, non-dihydropyridines, low-ceiling diuretics, corticosteroids, weight loss drugs, different classes of diabetes medications, frailty, and calendar year of index date. The PS from the model was then used to match each SGLT2i patient with other GLD patients in a 1:1 ratio, with a caliper width of 0.2. The validity of PS-matching was assessed by evaluating the standardized mean differences in patient characteristics. A >10% standardized mean difference between the two groups after matching was considered a nonnegligible imbalance. Comparisons of time to clinical events of interest from index date between the SGLT-2i and other GLD groups were performed by calculating hazard ratios and 95% confidence intervals using Cox proportional hazard models for the matched group. In addition, the number of occurrences of each event and the event rate per 1000 person-years were calculated. All statistical analyses were performed using SAS Viya® 3.5 (SAS Institute, Cary, NC, USA).

Fig. S2. Patient disposition



GLD, glucose-lowering drugs; SGLT2i, sodium–glucose cotransporter 2 inhibitors.

Table S4. Patient characteristics after propensity score matching

	Propensity score-matched cohorts		
	SGLT-2i group	Other GLD group	Standardized difference
Number of patients (N)	25,305	25,305	
Demographic characteristics			
Age, years（SD）	58.5（13.4）	59.1（14.4）	<0.01
Sex, n (%)			
Male	15,187 (60.0)	15,228 (60.2)	<0.01
Female	10,118 (40.0)	10,077 (39.8)	<0.01
Cardiovascular disease	162 (0.6)	338 (1.3)	0.07
Chronic kidney disease	56 (0.2)	163 (0.6)	0.06
Comorbidities, n (%)			
Cancer	3331 (13.2)	3392 (13.4)	<0.01
Chronic obstructive pulmonary disease	241 (1.0)	259 (1.0)	<0.01
Medications, n (%)			
Metformin	7096 (28.0)	7818 (30.9)	0.06
Sulfonylurea	4530 (17.9)	4971 (19.6)	0.04
Dipeptidyl peptidase-4 inhibitors	14,304 (56.5)	15,761 (62.3)	0.12
Glucagon-like peptide-1 receptor agonists	1081 (4.3)	1095 (4.3)	<0.01
Glinides	406 (1.6)	409 (1.6)	<0.01
Glitazones	1832 (7.2)	1993 (7.9)	0.02
α-glucosidase inhibitors	2016 (8.0)	2178 (8.6)	0.02
Insulins	7101 (28.1)	6927 (27.4)	0.02
Treatment for CVD risk	16,123 (63.7)	16,384 (64.7)	0.02
Low-dose acetylic salicylic acid	492 (1.9)	560 (2.2)	0.02
Statins	8262 (32.6)	8768 (34.6)	0.04
Angiotensin-converting enzyme inhibitors	586 (2.3)	659 (2.6)	0.02
Angiotensin II receptor blockers	8349 (33.0)	8883 (35.1)	0.04
Dihydropyridines calcium channel blockers	6317 (25.0)	6911 (27.3)	0.05
Low-ceiling diuretics (thiazide diuretics)	436 (1.7)	456 (1.8)	<0.01
Beta-blockers	1355 (5.4)	1449 (5.7)	0.02
High-ceiling diuretics (loop diuretics)	887 (3.5)	967 (3.8)	0.02
Warfarin	91 (0.4)	130 (0.5)	0.02
P2Y12 receptor antagonists	296 (1.2)	317 (1.3)	<0.01

CVD, cardiovascular disease; GLD, glucose-lowering drugs; SD, standard deviation; SGLT2i, sodium–glucose cotransporter 2 inhibitor.

Appendix 3. *Ad hoc* analysis for treatment costs

Treatment costs for CKD, HF, MI, and stroke in Japanese clinical settings were calculated in patients with T2DM and those without DM using a claims database as follows [7].

In total, 3777 (T2DM) and 3866 (non-DM) patients were analyzed (Fig. S3). Treatment costs including medication costs were calculated for each cardiorenal disease during the 36-month period after the incidence of the disease of interest (Table 5). The 36-month period consisted of an initial (first 12 months) and maintenance phase (24 months following the initial phase).

1. Data sources

The MDV database was used in this analysis and the data period was from April 2008 to September 2018 [7].

2. Analysis populations

All patients identified as having T2DM between April 2008 and September 2018 in the MDV database and patients who met the inclusion/exclusion criteria shown below in the database comprised the analysis population. The ICD-10 codes for defining diseases were described in Kadowaki et al. [7]. A cohort comprising an age/sex-matched control population (non-DM cohort) was also built. To build a non-DM cohort, we extracted the patients who had no diagnosis record of diabetes in the MDV database in the same period (from April 2008 to September 2018). The following conditions were applied to match the patients: 1) Having been treated at the same hospital (facility ID), 2) recorded sex (male or female), 3) age (case: at initial T2DM diagnosis, control: at initial hospital record), and 4) month and year (case: at initial T2DM diagnosis, control: at initial hospital record). Patients were selected by non-restoration sampling with a matching ratio of 1:2.

Inclusion criteria:

• Patients with a T2DM diagnosis during the study period (this criterion was for the T2DM cohort only)
• Patients with at least 1 year of follow-up from the first visit
• Patients ≥18 years old on the index date
• Patients with at least one of the following after the index date: HF, MI, stroke, and CKD.

Exclusion criteria:

• Patients with a T1DM diagnosis
• Patients with gestational diabetes within 1 year before the index date
• Patients without age/sex-matched patients in the database
• Patients with any cardiovascular or renal disease at the index date or within 12 months before the

index date (CKD, HF, MI, unstable angina, angina pectoris, atrial fibrillation, stroke, peripheral artery disease [PAD])

• Patients who developed the following diseases as the first cardiovascular or renal complication after the index date: unstable angina, angina pectoris, atrial fibrillation, PAD

• Patients who developed two or more cardiovascular or renal complications on the same day as the first cardiovascular or renal complication after the index date.

3. Index date

The index date of patients in the T2DM cohort was set as the first visit after 12 months from the initial hospital record date or the date of initial diagnosis of T2DM, whichever came later. The index date of patients in the non-DM cohort was set as the first visit after 12 months from the initial hospital record date.

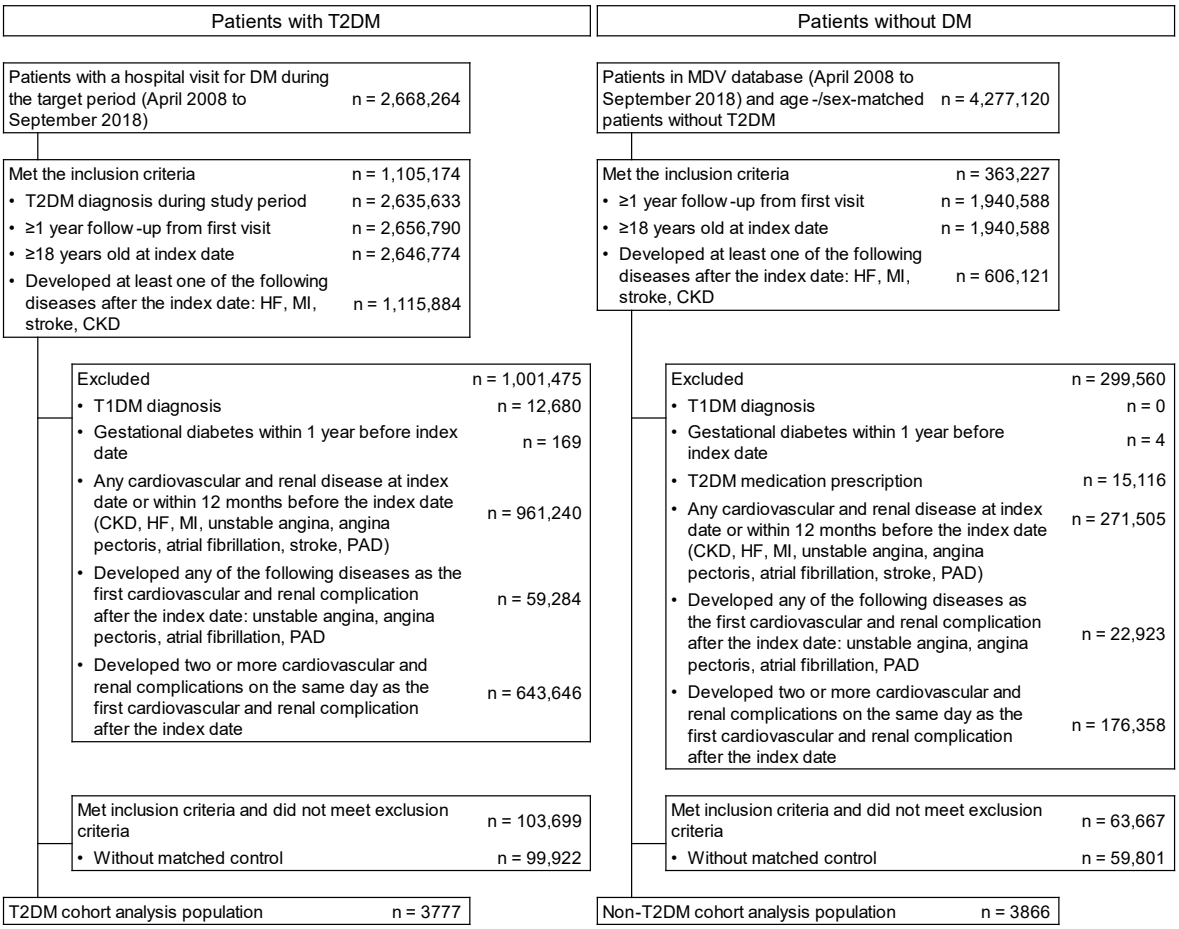
4. Outcome variables

Treatment costs for patients who developed one of HF, MI, stroke, or CKD in the follow-up period were summarized. The costs consisted of all money spent on the treatment including inpatient and outpatient costs, and were calculated as total cost including medication cost after a diagnosis of HF, MI, stroke, or CKD. These costs were calculated in initial and maintenance phases. The initial phase was defined as the first 12 months after a diagnosis of a particular cardiorenal comorbidity (HF, MI, stroke, or CKD), and the maintenance phase was defined as the 24-month period following the initial phase. Follow-up was stopped when the patient had a diagnosis of other cardiovascular or renal diseases (CKD, HF, MI, unstable angina, angina pectoris, atrial fibrillation, stroke, or PAD), any hospitalization, loss to follow-up, death, or September 2018 (whichever occurred first during the 36-month period). Both initial and maintenance costs were presented as an annual cost (cost/follow-up year).

5. Statistical analysis

Total cost in the initial and maintenance phases was summarized for the T2DM and non-DM cohorts in patients with each cardiorenal disease (HF, MI, stroke, or CKD). Patients with a total cost of zero were excluded from these analyses.

Fig. S3. Patient disposition



CKD, chronic kidney disease; DM, diabetes mellitus; HF, heart failure; MDV, Medical Data Vision; MI, myocardial infarction; PAD, peripheral artery disease; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Appendix 4.

Table S5. Age- or sex-dependent increases in risks of complication development

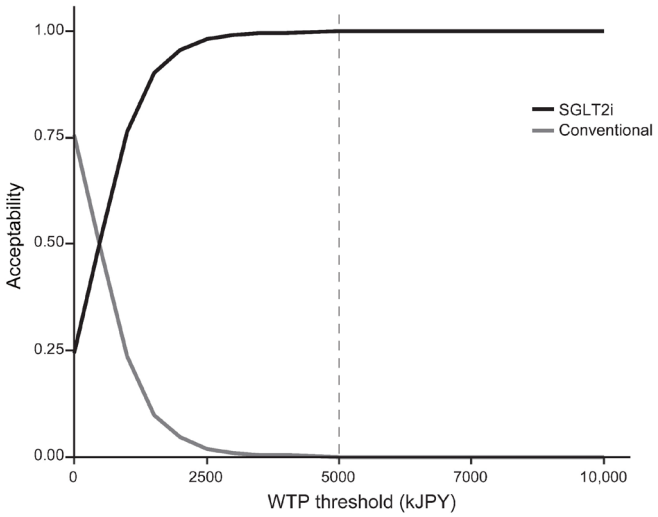
T2DM population			
Disease	**Age, HR {95% CI}**	**Sex, HR {95% CI}**	**Source**
CKD	Age per 1 y, 1.03 {1.02–1.04}	Male, 1.02 {0.83–1.26}	9
MI	Age 40–65, 1 (Reference) Age 66–74, 1.04 {0.75–1.45} Age 74–85, 2.17 {1.51–3.11} Age ≥85, 3.88 {2.60–5.78}	Female, 0.54 {0.42–0.70}	8
Stroke	Age 40–65, 1 (Reference) Age 66–74, 1.23 {1.02–1.50} Age 74–85, 2.49 {2.01–3.08} Age ≥85, 4.45 {3.53–5.61}	Female, 0.68 {0.59–0.79}	8
HF	Age 40–65, 1 (Reference) Age 66–74, 1.40 {1.11–1.75} Age 74–85, 2.84 {2.23–3.60} Age ≥85, 5.68 {4.40–7.33}	Female, 0.69 {0.59–0.81}	8
ESRD	Age per 10 y, 0.90 {0.82–0.99}	Male, 1.03 {0.82–1.28}	10
Non-DM CKD population			
Disease	**Age, HR {95% CI}**	**Sex, HR {95% CI}**	**Source**
MI	Age 18–59, 1 (Reference) Age 60–79, 1.659 {1.21–2.28} Age ≥80, 1.883 {1.35–2.64}	Female, 0.567 {0.50–0.64}	11
Stroke	Age per 1 y, 1.0 {1.02–1.06}	Male, 1.2 {0.84–1.74}	12
HF	Age per 1 y, 1.073 {1.036–1.112}	Male, 1.158 {0.567–2.364}	13
ESRD	Age per 10 y, 0.90 {0.82–0.99}	Male, 1.03 {0.82–1.28}	10

CI, confidence interval; CKD, chronic kidney disease; ESRD, end-stage renal disease; HF, heart failure; HR, hazard ratio; MI, myocardial infarction; non-DM, non-diabetes mellitus; T2DM, type 2 diabetes mellitus; y, year.

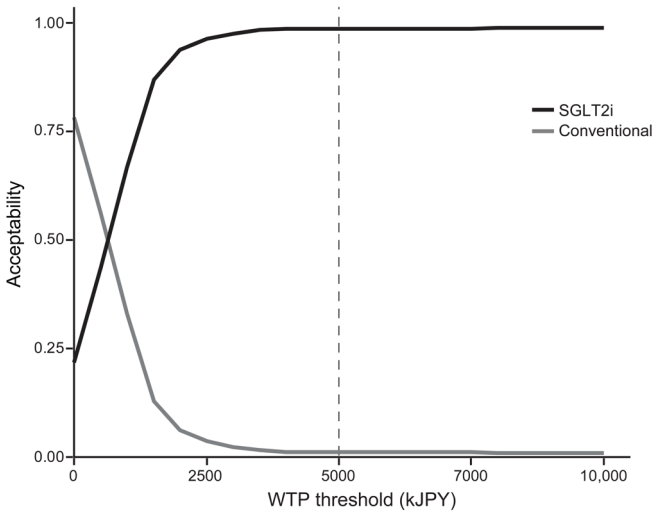
Appendix 5.

Fig. S4. Cost-effectiveness acceptability curve

A.



B.



The probability of the SGLT2i treatment or the conventional treatment being cost-effective at a given WTP level in the T2DM (A) and non-DM CKD (B) models. The dotted line represents the WTP threshold of JPY 5,000,000/QALY.

CKD, chronic kidney disease; kJPY, 1000 Japanese yen; non-DM, non-diabetes mellitus; QALY, quality-adjusted life years; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T2DM, type 2 diabetes mellitus; WTP, willingness-to-pay.

Appendix 6. Results of exploratory analyses

Table S6. Exploratory analysis for T2DM with CKD

	SGLT2i treatment	**Conventional treatment**	**Difference**
Cost, JPY	3,109,838	3,286,059	−176,221
QALY	6.388	6.248	0.140
LY	7.217	7.118	0.098
ICER/QALY			**Dominant**
Breakdown of costs, JPY			
Medication	444,776	278,952	165,824
CKD	1,478,856	1,372,365	106,490
HF	127,224	185,378	−58,154
MI	12,319	20,393	−8074
Stroke	29,644	52,293	−22,649
ESRD	1,017,019	1,376,678	−359,659

The results show the T2DM population with concomitant CKD. Difference is SGLT2i treatment − Conventional treatment.

CKD, chronic kidney disease; ESRD, end-stage renal disease; HF, heart failure; ICER, incremental cost-effectiveness ratio; JPY, Japanese yen; LY, life years; MI, myocardial infarction; QALY, quality-adjusted life years; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T2DM, type 2 diabetes mellitus.

Table S7. Exploratory analysis for CKD diagnosis rate

CKD diagnosis rate	**Two-fold increase**			**Five-fold increase**		
	SGLT2i treatment	**Conventional treatment**	**Difference**	**SGLT2i treatment**	**Conventional treatment**	**Difference**
Cost, JPY	899,903	849,268	50,635	1,269,086	1,305,924	−36,837
QALY	7.055	6.878	0.177	6.964	6.775	0.189
LY	7.533	7.377	0.156	7.497	7.341	0.156
ICER			**285,725**			**Dominant**
Breakdown of costs, JPY						
Medication	478,802	301,442	177,360	474,887	298,305	176,583
CKD	203,208	226,444	−23,236	458,236	498,905	−40,668
HF	89,282	106,164	−16,883	94,930	119,300	−24,370
MI	11,848	13,839	−1991	12,013	15,025	−3012
Stroke	32,170	54,104	−21,933	32,007	53,937	−21,930
ESRD	84,593	147,275	−62,682	197,013	320,452	−123,439

The results of the analysis assuming a two- or five-fold higher CKD diagnosis rate in the T2DM population.

Difference is SGLT2i treatment − Conventional treatment.

CKD, chronic kidney disease; ESRD, end-stage renal disease; HF, heart failure; ICER, incremental cost-effectiveness ratio; JPY, Japanese yen; LY, life years; MI, myocardial infarction; QALY, quality-adjusted life years; SGLT2i, sodium–glucose cotransporter 2 inhibitor; T2DM, type 2 diabetes mellitus.

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