Cost-effectiveness Analysis of Empagliflozin in Japan Based on Results From the Asian subpopulation in the EMPA-REG OUTCOME Trial

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ABSTRACT

Purpose: The goal of this study was to assess the cost-effectiveness of empagliflozin in Japan based on the Asian subpopulation in the EMPA-REG OUTCOME trial.

Methods: The trial has shown a reduction in the risk for cardiovascular (CV) and renal events with empagliflozin in patients with type 2 diabetes mellitus and established CV disease. A cost-effectiveness analysis based on the overall population of the EMPA-REG OUTCOME trial was reported previously by using a lifetime discrete event simulation model. The same modeling frame was adapted to evaluate the cost-effectiveness of treatment with empagliflozin added to standard of care (SoC) compared with SoC alone in Japan. The time to relevant clinical events and the hazard ratios were derived from an Asian subpopulation in the EMPA-REG OUTCOME trial. The costs for each event were estimated from a Japanese medical claims database. Direct medical costs, life expectancy, and quality-adjusted life years (QALYs) were calculated from the public health care perspective.

Findings: Treatment with empagliflozin was estimated to increase life expectancy by 6.2 years and 2.7 QALYs, whereas total cost increased by 1,115,475 yen compared with treatment with SoC alone. The incremental cost-effectiveness ratio was 415,849 yen/QALY. In the sensitivity analysis, there was no case that was in excess of the reference value of the incremental cost-effectiveness ratio in the pilot introduction for price revision in Japan (ie, 5 million yen/QALY).

Implications: Based on the Asian subpopulation in the EMPA-REG OUTCOME trial, our results suggest that empagliflozin added to SoC is highly cost-effective compared with SoC alone in Japan. (*Clin Ther*. 2019;41:2021–2040)

Key words: cost-effectiveness analysis, diabetes, EMPA-REG OUTCOME trial, empagliflozin, SGLT2 inhibitor.

INTRODUCTION

In a recent report, the number of people with diabetes in Japan was estimated at ~10 million, and 16.3% male adults and 9.3% female adults are strongly suspected

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as having diabetes based on their glycosylated hemoglobin value (≥6.5%) or family history.[1] The annual medical care expenditure for the treatment of diabetes in Japan totals ~1.24 trillion yen and accounts for ~4% of the total national medical costs.[2] It is important to note that this figure includes costs for glucose-lowering medications, but it does not include the additional financial burden incurred for the management of diabetes-related complications.

Diabetic complications are classified as macrovascular (cardiovascular [CV] diseases) and microvascular (diabetic retinopathy, nephropathy, and neuropathy). The risk of CV diseases is 2−3 times higher in patients with type 2 diabetes mellitus (T2DM) than in nondiabetic individuals,[3] and CV death is one of the major causes of mortality in this patient population.[4] In addition, diabetic nephropathy has emerged as the most common disease requiring hemodialysis; this, in turn, adds an additional lifelong medical expense.[5] Overall, diabetes and its related comorbidities have a hugely negative impact on patients as individuals and contribute to a broad socioeconomic burden in Japan.

Sodium glucose co-transporter 2 (SGLT2) is expressed in the proximal renal tubules and mediates ~90% of glucose reabsorption in the kidney. SGLT2 inhibitors are novel, oral, antidiabetic drugs that suppress glucose reabsorption, promote glucose excretion into the urine, and may alter sodium and water handling of the body. Empagliflozin is a highly selective SGLT2 inhibitor[6] and has been approved as a treatment for T2DM in ~100 countries, including Japan, Europe, and the United States.[7] In the EMPA-REG OUTCOME trial, the incidence of major adverse CV events was significantly reduced in the empagliflozin group compared with the placebo group in patients with T2DM and established CV disease.[8,9] Based on a subgroup analysis of Asian patients in the EMPA-REG OUTCOME trial (n = 1517), the reductions in the risk of CV outcomes and all-cause mortality with the empagliflozin group compared with the placebo group were consistent between the Asian subpopulation and the overall patient population.[10]

From a socioeconomic perspective, when assessing the overall cost-effectiveness of a treatment, it is important to include the impact of a potential reduction in the risk of future disease complications. In practical terms, to fully assess the impact of a disease on medical budgets, the cost of the drug itself and associated additional treatment should be considered together.

Health care systems and the health outcome of patients are key determinants of overall cost-effectiveness. Empagliflozin has shown consistent cost-effectiveness in previous analyses based on the overall population in the EMPA-REG OUTCOME trial in several key health care systems (the United States, the United Kingdom, Greece, and Italy).[11−14] The current study investigated the cost-effectiveness of empagliflozin in Japan by assessing the Asian subpopulation including Japanese patients from the EMPA-REG OUTCOME trial and the associated medical costs for diabetic complications.

PATIENTS AND METHODS

Modeling Framework

According to the International Society for Pharmacoeconomics and Outcomes Research−Society for Medical Decision Making (ISPOR-SMDM) Modeling Good Research Practices Task Force, the discrete event simulation model is a particularly good model to assess multiple and competing risks.[15] Furthermore, the discrete event simulation model has been used for cost-effectiveness analyses in CV diseases.[16] Thus, the discrete event simulation model was used to evaluate the cost-effectiveness of treatment with empagliflozin added to standard of care (empagliflozin plus SoC) compared with SoC alone in patients with T2DM and established CV disease in the United States, the United Kingdom, Greece, and Italy.[11−14] We used the same modeling framework but adapted it for a cost-effectiveness analysis in Japan based on Asian subpopulation data by including Japanese patients from the EMPA-REG OUTCOME trial.

To predict the incidence of potential CV and renal events in the lifetime of a patient beyond the median follow-up period of 3.1 years in the trial, we performed an event-free survival analysis regarding the time to 9 possible CV and renal events (CV death, nonfatal myocardial infarction [MI], nonfatal stroke, hospitalization for unstable angina [UA], hospitalization for heart failure [HF], transient ischemic attack, revascularization, albuminuria, and composite renal outcome [defined as a decrease in

estimated glomerular filtration rate by 40%, the need for renal replacement therapy, or renal death]). Lifetime risk was estimated by using the discrete event simulation model based on a parametric time-to-event curve for each estimated potential event. Each time to the possible CV or renal events was predicted from the parametric time-to-event curves, and each simulated patient experienced the event which occurs first. For example, if it was estimated that the time to event of nonfatal MI was 3 years, nonfatal stroke was 2 years, and hospitalization for UA was 8 years, the stroke with the earliest time to event was recorded as an event in the simulation.

In addition, genital infections associated with SGLT2 inhibitors and deaths other than CV death were incorporated into the model. The 8-step simulation process using the discrete event simulation model was described previously[11–14] and is shown in Figure 1. A total of 10,000 patients were simulated for base case analysis.

Asian Subgroup Analysis of the EMPA-REG OUTCOME Trial

The EMPA-REG OUTCOME trial was a multicenter, randomized, double-blind, placebo-controlled study that examined the effects of empagliflozin compared with placebo on CV morbidity and mortality in patients with T2DM and established CV disease from several regions (ie, North America, Australia, New Zealand, Latin America, Europe, Africa, Asia). In the trial,[8,10] investigators were encouraged to adjust glucose-lowering therapy at their discretion to achieve glycemic control (after 12 weeks) and CV risk factors according to local guidelines, including Japanese guidelines.[17] In the overall population (N = 7020) of the EMPA-REG OUTCOME trial, the incidence of major adverse CV events (MACE), including CV death, nonfatal MI, and nonfatal stroke, was significantly reduced in the empagliflozin group compared with the placebo group in patients with

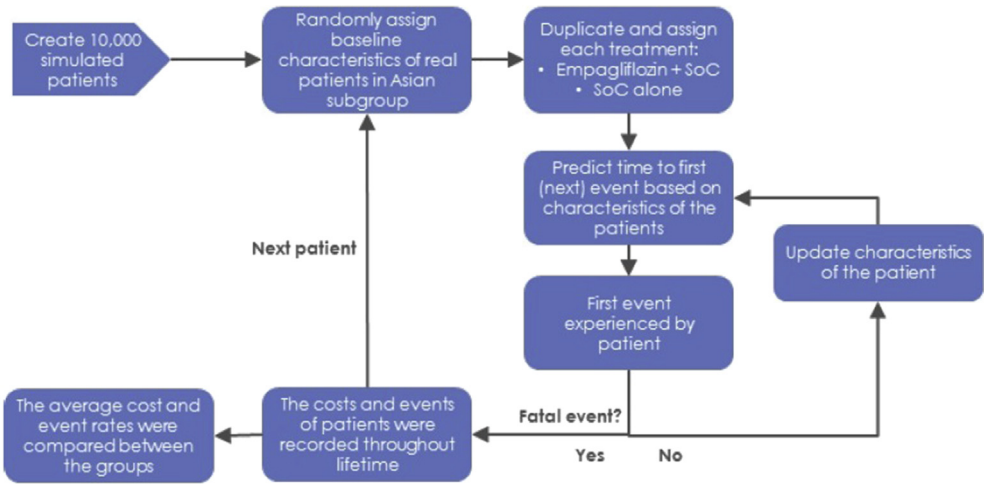


Figure 1. Patient-level simulation flow. The 8-step simulation process using the discrete event simulation model is shown. (1) A total of 10,000 simulated patients were randomly assigned with baseline characteristics of real patients in the EMPA-REG OUTCOME trial. (2) Each patient is duplicated and assigned to each treatment: empagliflozin plus standard of care (SoC) or SoC alone. (3) Each time to the possible cardiovascular or renal events was predicted from the parametric time-to-event curve based on the characteristics (eg, age, sex, disease history, previous events) of each simulated patient. (4) Each simulated patient experiences the event which occurs first. (5) The characteristics of each patient were uploaded. (6) Processes #3 through #5 were repeated until a fatal event occurred in the simulated patients. (7) The costs and events of each simulated patient were recorded throughout their lifetime. (8) The average cost and event rates were compared between the empagliflozin plus SoC group and the SoC alone group.

T2DM and established CV disease (hazard ratio in the empagliflozin group, 0.86; 95.02% CI, 0.74−0.99; $P < 0.001$ for noninferiority and $P = 0.04$ for superiority). In addition, all-cause mortality, hospitalization for HF, and the incidence or worsening of nephropathy occurred less frequently in the empagliflozin group compared with the placebo group.[9,10]

In the EMPA-REG OUTCOME trial, the reduction in MACE in 1517 Asian patients (21.6%) was consistent with the overall population (hazard ratio in the Asian patients, 0.68 [95% CI, 0.48−0.95]; P value for treatment interaction by race [Asian, white, black/African-American] = 0.0872). The effects of empagliflozin on the components of MACE, all-cause mortality, and heart failure outcomes were also consistent between the overall population and Asian patients (P values for race interaction, >0.05).[11] Table I shows the patient characteristics from the simulation results based on the Asian subpopulation in the EMPA-REG OUTCOME trial.

Parameters

Time to Potential Events

The time to each event was estimated by using the event-free survival curve modeled by the parametric curve that fits the Kaplan−Meier curve of each event in the Asian subpopulation, including Japanese subjects, in the EMPA-REG OUTCOME trial. Six parametric curves (exponential, Weibull, log-normal, log-logistic, generalized gamma, and Gompertz distributions) were tested for each CV and renal event. When estimating the parametric curve of each event, if another event or death occurred, it was taken as censoring.

The fittings between parametric curves and the Kaplan−Meier curves were assessed by using the Akaike information criterion, the Bayesian information criterion, and consistency with the visual inspection between the 2 curves (see the Supplemental Table and Supplemental Figures 1−9 in the online version at https://doi.org/10.1016/j.clinthera.2019.07.016).

Table I. Simulation results of patient characteristics based on the Asian subpopulation in the EMPA-REG OUTCOME trial.

Patient Parameter	Values
Demographic characteristics	
Age, y	60.9
Female sex	26.9%
BMI ≥30 kg/m^2	16.2%
Glycosylated hemoglobin ≥8.5%	30.1%
CV history	
History of stroke	25.5%
History of MI	40.1%
History of CABG	14.6%
History of MCAD	54.9%
History of SVCAD	11.1%
History of PAD	10.2%
Renal history	
eGFR 60−90 mL/min (mild)	51.4%
eGFR <60 mL/min (moderate/severe)	25.6%

BMI = body mass index; CABG = coronary artery bypass grafting; eGFR = estimated glomerular filtration rate; MCAD = multivessel coronary artery disease; MI = myocardial infarction; PAD = peripheral artery disease; SVCAD = single vessel coronary artery disease.

Baseline and time-dependent predictors that affect the risk of the clinical events were tested for significance in the risk equations. Each potential predictor such as demographic information, baseline biomarkers, event history at baseline, and CV/renal events during the trial was assessed according to a univariate model to determine whether it was associated with the clinical events. This was done by including the variable in a regression model on its own and assessing the magnitude and statistical significance of the effect estimate. The relevance of the magnitude of the effect may be judged based on the effect of other predictors. Key variables known to be important prognostic factors were carried forward to the next step despite failing to meet the significance level (set at $P < 0.2$). Significant predictors were then combined in a multivariable regression model, which was then trimmed (one variable at a time) to exclude those not significant at $P < 0.2$. The final model only includes predictors that have a significant effect or important prognostic factors that show a nonnegligible effect size. The additional efficacy of empagliflozin was also considered as a covariate in the parametric curve estimation (Table II). In subsequent risk estimates in patients with nonfatal events, time to event was adjusted if the histories of the previous events had a statistically significant effect on subsequent event risk or were considered to be important prognostic factors.

The time to genital infection was estimated from the incidence in the Asian subpopulation of the EMPA-REG OUTCOME trial (empagliflozin plus SoC group, 2.21/100 patient-years; SoC alone group, 0.63/100 patient-years) using the Weibull distribution. The estimation for deaths other than CV death was made from the mortality reported by the Population Survey of Japan and the age of the simulated patient by using the Gompertz distribution.[18]

Utility Parameters

The baseline utility and utility decrements for each event were extracted from a previous report in which utility reductions for CV and renal diseases were studied in the United Kingdom by using the 3-level version of the EQ-5D (Table III).[19] However, the utility decrements with revascularization, hospitalization for UA, and the initiation of dialysis were not available from the report. Therefore, the disutility with hospitalization for UA was assumed to be the same as that with nonfatal MI. The decrement with revascularization was derived from another report.[20] The utility decrement by initiation of dialysis referred to a Japanese report in which the decrement was assessed in 24 Japanese patients with dialysis using the 5-level version of the EQ-5D.[21] The baseline utility weight and utility weight with initiation of dialysis were 0.719[19] and 0.749,[21] respectively; the relationship between these utility weight analyses has not been assessed for statistical and clinical significance. The disutility for the composite renal outcomes remained unclear. Therefore, in this base case analysis, it was assumed to be 0 and considered only the cost from the conservative perspective for empagliflozin, but the impact of this assumption was tested in a sensitivity analysis.

Cost Parameters

In this analysis, the only costs considered were direct medical costs from the public health care perspective (eg, including patient copayment) in Japan. The cost of treatment for each potential event was calculated in patients with T2DM and established CV disease by using EBM Provider (provided by Medical Data Vision Co, Ltd, Tokyo, Japan), a Japanese database consisting of the medical claims data from 323 emergency care facilities (hospitals using the Diagnosis Procedure Combination [DPC] payment system) in Japan. It covers ~19% of hospitals with the DPC payment system (so-called DPC hospitals) in Japan and was not biased regarding region, age, or sex.[22] The medical service information of ~208,000 patients has been accumulated in the database as of December 2017 (Table IV).

In this analysis, the cost of treatment was estimated from the mean fee-for-service cost for each potential event if the event was recorded as both the disease (requiring hospitalization) and the diseases/comorbidities actually requiring subsequent medical resources (Figure 2). The details of the subject population and the definitions of each event were defined based on the inclusion/exclusion criteria of the EMPA-REG OUTCOME trial (Table V). Characteristics of analyzed patients for the cost of CV and renal events are shown in Table VI.

Table II. Risk equations predicting time to potential clinical events.

Parameters	Estimate of Coefficient								
Clinical Event	Non-fatal MI	Non-fatal stroke	Hospitalization for UA	Hospitalization for HF	Transient ischemic attack	Revascularization	Progression of albuminuria	Composite renal outcome	CV death
Statistical Distribution	Exponential	Weibull	Exponential	Weibull	Exponential	Exponential	Weibull	Exponential	Weibull
Shape	1.000	0.920	1.000	0.701	1.000	1.000	1.146	1.000	1.191
Log (scale)	4.709	5.404	5.604	10.737	5.980	4.475	1.430	5.423	4.464
Coefficients: baseline patient characteristics									
Age >= 65	-0.003	-0.080	-0.766	-0.425	-0.512	0.174	0.110	-0.821	0.451
Female	-	-	-	-	-	-0.737	0.258	-	-
BMI >= 30	-	-	-	0.866	-	-	-0.173	-0.926	-0.927
HbA1c >= 8.5	-	-	-	-	-	0.450	-	-0.493	-
History of Stroke	-	0.905	-0.844	0.738	-	-0.869	0.187	-	-
History of CABG	-	-	-	-	-	-	-	-	-1.160
History of MCAD	0.597	-	0.873	-	-	0.656	-	-	-
History of PAD	-	0.596	-	-	-	-	0.242	0.894	-
Renal impairment: Moderate/severe (eGFR < 60)	-	0.702	1.046	2.259	-	-	0.171	1.517	-
Renal impairment: Mild (eGFR 60-90)	-	-0.077	0.463	1.925	-	-	-0.051	0.491	-
Treated with empagliflozin	-0.344	0.035	-0.062	-0.098	-1.124	0.082	-0.219	-0.784	-0.886
Coefficients: events in trial									
Non-fatal MI	-	1.766	-	2.521	-	3.120	-	-	-
Non-fatal stroke	-	-	-	-	-	-	-	-	1.950
Hospitalization for UA	1.030	-	-	-	-	-	-	-	-
Hospitalization for HF	-	-	-	-	-	-	-	-	1.685
Revascularization	-	-	1.068	-	-	-	-	-	-
Progression of albuminuria	-	-	-	1.312	-	-	-	1.499	1.415

Table II. (*Continued*)

Parameters	Estimate of Coefficient								
Clinical Event	Non-fatal MI	Non-fatal stroke	Hospitalization for UA	Hospitalization for HF	Transient ischemic attack	Revascularization	Progression of albuminuria	Composite renal outcome	CV death
Composite renal outcome	-	-	-	1.876	-	-	-	-	1.379

BMI = body mass index; CABG = coronary artery bypass grafting; CV = cardiovascular; eGFR = estimated glomerular filtration rate; HbA1c = glycosylated hemoglobin; HF = heart failure; MCAD = multivessel coronary artery disease; MI = myocardial infarction; PAD = peripheral artery disease; SVCAD = single-vessel coronary artery disease; UA = unstable angina.

The cost of the composite renal outcome was considered as the cost of dialysis/renal replacement therapy in the clinical setting in Japan. The cost was extracted from a previous survey in Japan[23] and weighted with the incidence of renal replacement therapy in a composite renal outcome in the Asian subpopulation of the EMPA-REG OUTCOME trial (2.15%, unpublished data).

The price of each dose of empagliflozin was set according to the National Health Insurance Drug Price List, and the weighted price was calculated by the percentage of use of each formula in Japan (empagliflozin 10-mg tablets, 89.4%; empagliflozin 25-mg tablets, 10.6% [unpublished data]) (Table VII). The costs of SoC were not considered because treatment with SoC was performed in both groups in the EMPA-REG OUTCOME trial. Therefore, the difference of initiation and discontinuation of background drugs such as rescue medication was not reflected within the analysis. This assumption leads to a conservative estimate for empagliflozin use, because additional glucose-lowering medications were required in the placebo group compared with the empagliflozin group to maintain blood glucose control.[11]

Because genital infections may affect patients' quality of life, we included disutility of genital infections in this analysis. However, the medical costs associated with genital infections were not expected to have a notable overall impact on total cost compared with those required to treat CV and renal events, and thus these were excluded.

Analytical Methods

The time horizon was defined as lifetime. The quality-adjusted life year (QALY) was used as a measurement of effectiveness. Analysis was performed from the public health care perspective, and only direct medical costs were considered. The discount rates for both the cost and effectiveness were 2% per year.[24]

Sensitivity Analyses

To investigate the magnitude of the impact of each parameter and the potential impact on the outcomes, a sensitivity analysis was conducted to assess the following: (1) which component had the highest impact during treatment with empagliflozin (nine possible CV and renal events); (2)

Table III. Utility decrements for each event.

Parameter	Values	SE	Source
Baseline utility weight	0.719	Unreported	Sullivan and Ghushchyan,[19] 2016
Disutility of each potential event			
Nonfatal MI	−0.047	0.005	Sullivan and Ghushchyan,[19] 2016
Nonfatal stroke	−0.060	0.007	Sullivan and Ghushchyan,[19] 2016
Hospitalization for UA	−0.047	0.005	Assumed same as MI
Hospitalization for HF	−0.050	0.007	Sullivan and Ghushchyan,[19] 2016
Transient ischemic attack	−0.070	0.031	Sullivan and Ghushchyan,[19] 2016
Revascularization	−0.030	Unreported	Lindgren et al,[20] 2007
Progression of albuminuria	−0.038	0.011	Sullivan and Ghushchyan,[19] 2016
Composite renal outcome	0.000	—	Assumption
Adverse event			
Genital infection	−0.038	0.008	Sullivan and Ghushchyan,[19] 2016

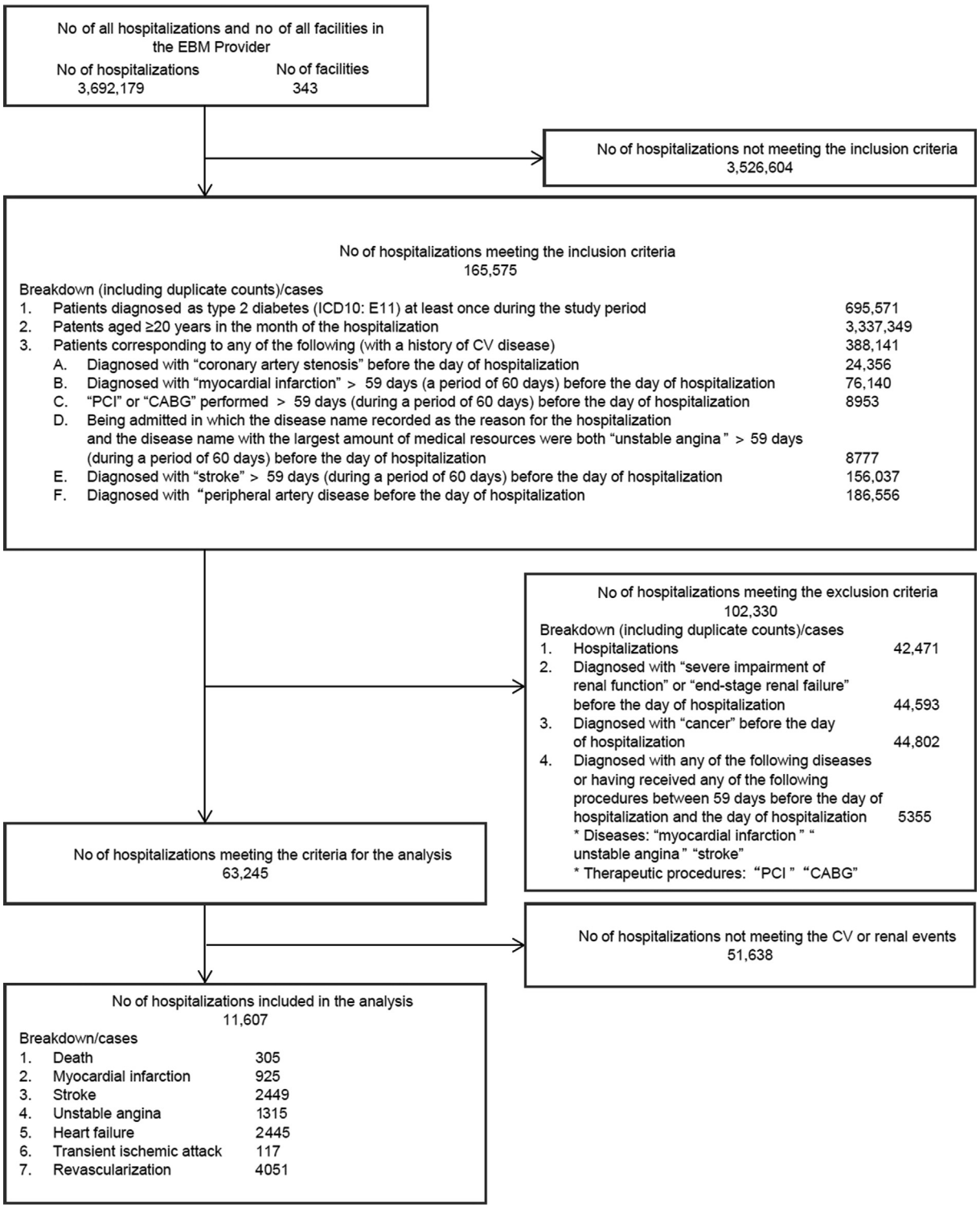
HF = heart failure; MI = myocardial infarction; UA = unstable angina.

Table IV. Estimated treatment costs for cardiovascular (CV) and renal events.

Parameter	Mean	SD	Source
Nonfatal MI	657,905 yen	903,760 yen	EBM Provider
Nonfatal stroke	1,390,238 yen	1,425,531 yen	
Hospitalization for UA	777,680 yen	1,012,291 yen	
Hospitalization for HF	1,055,068 yen	1,036,802 yen	
Transient ischemic attack	472,088 yen	541,858 yen	
Revascularization	1,486,172 yen	1,241,864 yen	
Progression of albuminuria	0 yen	—	Assumption
Composite renal outcome	102,657 yen	—	Survey report of dialysis medical expenses, EMPA-REG OUTCOME trial; 4,773,540 yen/year × 2.15%
CV death	1,629,280 yen	2,158,163 yen	EBM Provider
Genital infection	0 yen	—	Assumption

CV = cardiovascular; EMPA-REG OUTCOME = Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes; HF = heart failure; MI = myocardial infarction; UA = unstable angina.

the effect of time horizon due to the uncertainties of long-term modeling, and (3) the impact of the disutility for dialysis (renal replacement therapy, which is known to be expensive) on QALY and incremental cost-effectiveness ratio (ICER). As for the disutility for dialysis, the value (−0.156) was obtained by subtracting the utility weight at the age of 60−69 years (0.905; average value, 60−69 years, male and female)[25] from the utility weight of patients with dialysis at the same age (0.749).[21] In addition, a one-way sensitivity analysis was performed to create a single tornado diagram using each specific parameter (eg, change all disutility at once). Survival parameters were excluded from the one-way sensitivity analysis because 2 required parameters (scale and shape parameters) should be simultaneously changed to generate a realistic survival curve based on a variance−covariance matrix. The range of change in the parameters was 0%−4% for the discount rate and ±20% of the base case value for the other parameters. Furthermore, a probabilistic sensitivity


No of all hospitalizations and no of all facilities in the EBM Provider
No of hospitalizations 3,692,179
No of facilities 343
No of hospitalizations not meeting the inclusion criteria 3,526,604
No of hospitalizations meeting the inclusion criteria 165,575
Breakdown (including duplicate counts)/cases
1. Patients diagnosed as type 2 diabetes (ICD10: E11) at least once during the study period 695,571
2. Patents aged ≥20 years in the month of the hospitalization 3,337,349
3. Patients corresponding to any of the following (with a history of CV disease) 388,141
A. Diagnosed with "coronary artery stenosis" before the day of hospitalization 24,356
B. Diagnosed with "myocardial infarction" > 59 days (a period of 60 days) before the day of hospitalization 76,140
C. "PCI" or "CABG" performed > 59 days (during a period of 60 days) before the day of hospitalization 8953
D. Being admitted in which the disease name recorded as the reason for the hospitalization and the disease name with the largest amount of medical resources were both "unstable angina" > 59 days (during a period of 60 days) before the day of hospitalization 8777
E. Diagnosed with "stroke" > 59 days (during a period of 60 days) before the day of hospitalization 156,037
F. Diagnosed with "peripheral artery disease before the day of hospitalization 186,556
No of hospitalizations meeting the exclusion criteria 102,330
Breakdown (including duplicate counts)/cases
1. Hospitalizations 42,471
2. Diagnosed with "severe impairment of renal function" or "end-stage renal failure" before the day of hospitalization 44,593
3. Diagnosed with "cancer" before the day of hospitalization 44,802
4. Diagnosed with any of the following diseases or having received any of the following procedures between 59 days before the day of hospitalization and the day of hospitalization 5355
* Diseases: "myocardial infarction" "unstable angina" "stroke"
* Therapeutic procedures: "PCI" "CABG"
No of hospitalizations meeting the criteria for the analysis 63,245
No of hospitalizations not meeting the CV or renal events 51,638
No of hospitalizations included in the analysis 11,607
Breakdown/cases
1. Death 305
2. Myocardial infarction 925
3. Stroke 2449
4. Unstable angina 1315
5. Heart failure 2445
6. Transient ischemic attack 117
7. Revascularization 4051

analysis was performed with 1000 Monte Carlo simulations in 1000 patients to evaluate the uncertainty of the results. Regarding the probability distribution of each parameter, the cost parameters were assumed to have a gamma distribution and the utility to have a beta distribution.[26]

RESULTS

Absolute event rates and hazard ratios were comparable between the EMPA-REG OUTCOME trial and the model using a simulation for the median follow-up time of the trial. We consider that this finding validates the model, at least for the median follow-up period of the trial (data not shown).

Rates of CV death, progression of albuminuria, and composite renal outcomes were lower in the empagliflozin plus SoC group than in the SoC alone group (Table VIII). Although all-cause death was significantly lower in the empagliflozin plus SoC group than in the SoC alone group in the EMPA-REG OUTCOME trial, more simulated patients were estimated to have a non−CV death in the empagliflozin plus SoC group than in the SoC alone group. This finding is due to a reduction in competing risk (ie, CV death) with empagliflozin because every patient had a fatal event in this model.

Simulated patients achieved a 6.2-year increase in long-term survival with empagliflozin (mean 20.6 years in the empagliflozin plus SoC group vs 14.4 years in the SoC alone group) (Table IX). The empagliflozin plus SoC group had 10.7 QALYs and the SoC alone group had 8.0 QALYs, resulting in an increase of 2.7 QALYs with empagliflozin over a lifetime. The average cost for the events was reduced by 118,997 yen because the number of events was reduced by empagliflozin. Lifetime medication costs for empagliflozin were 1,234,473 yen, leading to an incremental cost for empagliflozin of 1,115,475 yen. Collectively, the ICER was 415,849 yen/QALY with empagliflozin plus SoC versus SoC alone.

The sensitivity analysis for the assumptions showed that the ICER ranged from 409,037 yen/QALY to 2,338,450 yen/QALY (Table X). The ICER was lower with increased treatment periods with empagliflozin (2,338,450 yen/QALY at 5 years; 725,255 yen/QALY at 10 years; 415,849 yen/QALY for life years) (Tables IX and X). Increased life years (6.2 years) with empagliflozin were attenuated by 1.5 or 6.3 years when the effect of empagliflozin on either CV death or renal composite outcome was adjusted to 0. These data from the model suggest that the longer term survival with empagliflozin is mainly due to a reduction in CV deaths. The ICER increased when the effect of empagliflozin on CV death was assumed to be 0 (1,214,694 yen/QALY).

The one-way sensitivity analysis revealed that the discount rate exerted the greatest effect on the results of the analysis (Figure 3). According to the one-way sensitivity analysis using data from overseas studies, including the baseline utility and disutility, ranged from 341,912 to 530,588 yen/QALY and from 406,613 to 425,515 yen/QALY, respectively.

Considering a potential ICER threshold of 5 million yen in the cost-effectiveness evaluation of the official re-pricing system in Japan, which the Central Social Insurance Medical Council introduced on a trial basis in 2016,[27] the probabilistic sensitivity analysis suggested that the probability of being cost-effective (ICER <5 million yen) exceeded 99% in the empagliflozin plus SoC group compared with the SoC alone group (Scatchard analyses) (Figure 4). Consistent with the base case result, the willingness-to-pay (WTP) was ~420,000 yen; the probability cost-effectiveness of empagliflozin plus SoC was considered adequate (exceeds 50%) (Figure 5).

DISCUSSION

We conducted a cost-effectiveness analysis of empagliflozin based on the Asian subpopulation in the EMPA-REG OUTCOME trial. The ICER of

Figure 2. Patient flow for cost analysis using EBM Provider. The cost of treatment for each cardiovascular (CV) and renal event was calculated in patients with type 2 diabetes mellitus and established CV disease by using EBM Provider, a Japanese claim database provided by Medical Data Vision Co, Ltd. The patients were extracted for this analysis by following inclusion/exclusion criteria from all hospitalizations between April 2016 and December 2017 (3,692,179), and the cost of treatment was calculated for 11,607 hospitalizations. CABG = coronary artery bypass grafting; ICD-10 = *International Classification of Diseases, Tenth Revision*; PCI = percutaneous coronary intervention.

Table V. Summary of definitions used for the selection of medical cost data from EBM Provider.

Database searched	EBM Provider
Study period	April 2016—December 2017
Facilities surveyed	Facilities that stored data during the period of analysis (storage period varies among facilities)
Subjects	• Hospitalized patients who were diagnosed with type 2 diabetes mellitus (ICD-10: E11) at least once during the period of analysis and had a history of the following potential events, and were admitted and discharged during the period of analysis. • However, patients who were diagnosed with MI, UA, or stroke, or who underwent PCI or CABG during the 60 days before the day of hospitalization and those diagnosed with liver disorder, severe impairment of renal function, end-stage renal failure, or cancer before the day of hospitalization were excluded.
Definitions of cardiovascular disease	
Coronary artery stenosis	ICD-10: I251 (atherosclerotic heart disease)
MI	ICD-10: I21 (acute myocardial infarction) ICD-10: I22 (recurrent myocardial infarction) ICD-10: I24 (other acute ischemic heart diseases) ICD-10: I251 (atherosclerotic heart disease) ICD-10: I259 (chronic ischemic heart disease, unspecified)
PCI	Procedure code: K546 (percutaneous coronary angioplasty) Procedure code: K547 (percutaneous coronary atherectomy) Procedure code: K548 (percutaneous coronary angioplasty [using a special catheter]) Procedure code: K549 (percutaneous coronary artery stenting)
CABG	Procedure code: K552 (coronary/aortic bypass grafting) Procedure code: K552-2 (coronary/aortic bypass grafting [not using artificial heart-lung machine])
UA	ICD-10: I200 (unstable angina)
Stroke	ICD-10: I60 (subarachnoid hemorrhage) ICD-10: I610 (intracerebral hemorrhage in hemisphere, subcortical) ICD-10: I611 (intracerebral hemorrhage in hemisphere, cortical) ICD-10: I613 (intracerebral hemorrhage in brain stem) ICD-10: I614 (intracerebral hemorrhage in cerebellum) ICD-10: I615 (intracerebral hemorrhage, intraventricular) ICD-10: I616 (intracerebral hemorrhage, multiple localized) ICD-10: I618 (other intracerebral hemorrhage) ICD-10: I619 (intracerebral hemorrhage, unspecified) ICD-10: I63 (cerebral infarction)
PAD	ICD-10: I702 (atherosclerosis of the limbs) ICD-10: I709 (systemic and unspecified atherosclerosis) ICD-10: I739 (peripheral vascular disease, unspecified) ICD-10: I742 (embolism and thrombosis of arteries of the upper extremities) ICD-10: I743 (embolism and thrombosis of arteries of the lower extremities)

(*continued on next page*)

Table V. (*Continued*)

Database searched	EBM Provider
	ICD-10: I744 (embolism and thrombosis of arteries of extremities, unspecified) ICD-10: I745 (embolism and thrombosis of iliac artery)
Definitions of potential events	
Death	Hospitalization in which "myocardial infarction," "stroke," heart failure," or "cardiogenic shock" was the disease on which the largest amount of medical resources were spent and in which death was the outcome at discharge
MI	Hospitalization in which the disease name recorded as the reason for the hospitalization and the disease name with the largest amount of medical resources were both "myocardial infarction" (except those in which death was the outcome at discharge)
Stroke	Hospitalization in which the disease name recorded as the reason for the hospitalization and the disease name with the largest amount of medical resources were both "stroke" (except those in which death was the outcome at discharge)
UA	Hospitalization in which the disease name recorded as the reason for the hospitalization and the disease name with the largest amount of medical resources were both "unstable angina" (except those in which death was the outcome at discharge)
HF	Hospitalization in which the disease name recorded as the reason for the hospitalization and the disease name with the largest amount of medical resources were both "heart failure" (except those in which death was the outcome at discharge)
Transient ischemic attack	Hospitalization in which the disease name recorded as the reason for the hospitalization and the disease name with the largest amount of medical resources were both "transient ischemic attack" (except those in which death was the outcome at discharge)
Revascularization	Hospitalizations other than the above in which "revascularization (procedure code: K552, K552−2, K546−K550-2)" was performed (except those in which death was the outcome at discharge)

CABG = coronary artery bypass grafting; HF = heart failure; ICD-10 = *International Classification of Diseases, Tenth Revision*; MI = myocardial infarction; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; UA = unstable angina.

empagliflozin plus SoC versus SoC alone from the base case analysis was 415,849 yen/QALY. In Japan, 2 previous studies reported a WTP for 1 QALY of 6.7 and 5 million yen.[28,29] Moreover, the reference value of ICER for drug price adjustment in the pilot introduction of cost-effectiveness evaluation in Japan was set at 5 to 10 million yen.[27] These Japanese reference values of ICER are comparable to those reported for other countries. For instance, in the United Kingdom, the National Institute for Health and Care Excellence, which issued a recommendation about the domestic reimbursement of health care technologies, explicitly stated in its guidelines for cost-effectiveness analysis that the threshold of the ICER is £20,000 to £30,000/QALY[30] (2.6−3.9 million yen/QALY [conversion rate, £1 = 130 yen]). In addition, the World Health Organization stated that a treatment was considered as "highly cost-effective" or "cost-effective" when it is lower than or 1 to 3 times the per capita gross domestic product (GDP), respectively[31] (4.25−12.75 million yen, estimated by Japanese GDP per person, 4.25 million yen in 2016[32]). The base case

Table VI. Patient characteristics of the population for cost analysis using EBM Provider.

Characteristic	Value
Demographic	
N	11,607
Mean age, y	73.0
Female sex, %	30.2
Mean BMI, kg/m^2	24.41
Mean HbA_{1c}, %	6.9
Mean eGFR, mL/min	59.4
CV history, %	
History of stroke	32.9
History of MI	26.6
History of CABG	0.7
History of CAD	72.4
History of PAD	37.3

BMI = body mass index; CABG = coronary artery bypass grafting; CAD = coronary artery disease; eGFR = estimated glomerular filtration rate; HbA_{1c} = glycosylated hemoglobin; MI = myocardial infarction; PAD = peripheral artery disease.

scenario and one-way sensitivity analyses consistently showed the ICER of empagliflozin was markedly lower than the aforementioned reference value, and the probabilistic sensitivity analysis showed that the ICER of empagliflozin being > 5 million yen was <1%. This result suggests that empagliflozin was highly cost-effective.

Diabetic nephropathy is the most common cause of severe renal failure and renal replacement therapy in Japan. Dialysis incurs one of the highest costs; in Japan, the cost for 1 month is estimated as ~400,000 yen for outpatient hemodialysis and 300,000 to 500,000 yen for continuous ambulatory peritoneal dialysis per patient.[33] In the EMPA-REG OUTCOME trial, empagliflozin significantly reduced progression of kidney disease and was consistent between the overall population and the Asian subpopulation. We therefore hypothesized that the cost of treatments for renal events, including dialysis, would have a significant impact on the cost-effectiveness of empagliflozin. However, it did not have a huge impact on the cost-effectiveness of empagliflozin. This outcome is likely because the number of patients who underwent renal replacement therapy (typically dialysis in Japan) was limited in the Asian subpopulation in the EMPA-REG OUTCOME trial. If empagliflozin shows benefit in the ongoing kidney outcome trial (EMPA-KIDNEY [The Study of Heart and Kidney Protection With Empagliflozin],[34] expected completion in 2022), it may be possible to evaluate a more precise impact of the dialysis treatment on the cost-effectiveness of empagliflozin and the impact on ICER values.

In a previous report in which the cost of medical care was analyzed by using claims data in 2002 before the introduction of the DPC payment system in Japan, the costs of treatment for MI (including fatal MI), UA, and stroke (ischemic alone) were estimated as 2.6, 1.9, and 1.5 million yen, respectively.[35] In a comparison between the previous report[35] and our analysis, a discrepancy was seen in the cost of treatments for MI and UA (0.7 and 0.8 million yen) but not for stroke (1.4 million yen). These differences were assumed to be related to changes in the medical environment from 2002, the

Table VII. Estimated costs for treatments.

Parameter	Values	Source
Empagliflozin cost/month	6501 yen	Monthly cost 213.6 yen × 30.4375 days/month
Weighted empagliflozin cost/day	214 yen	Weighted average of each cost and usage rate 198.7 yen × 89.4% + 339 yen × 10.6% = 213.6 yen
Empagliflozin, 10 mg/d	198.7 yen	National Health Insurance Drug Price List
Empagliflozin, 25 mg/d	339 yen	
Usage rate of empagliflozin, 10 mg	89.4%	Unpublished data
Usage rate of empagliflozin, 25 mg	10.6%	
Standard of care cost/month	0 yen	Assumed to be offset between the groups

Table VIII. Base case analysis result of clinical events (per 100 patient-years).

Clinical Event	Empagliflozin + Standard of Care	Standard of Care	Difference
Potential event			
Nonfatal MI	1.07	1.51	−0.44
Nonfatal stroke	1.44	1.47	−0.03
Hospitalization for UA	1.32	1.36	−0.04
Hospitalization for HF	1.29	1.77	−0.48
Transient ischemic attack	0.07	0.21	−0.14
Revascularization	1.74	1.97	−0.23
Progression of albuminuria	4.55	6.37	−1.82
Composite renal outcome	1.19	2.31	−1.12
CV death	3.02	5.56	−2.54
Non−CV death	1.82	1.37	0.45
Adverse event			
Genital infection	1.63	0.57	1.06

CV = cardiovascular; HF = heart failure; MI = myocardial infarction; UA = unstable angina.

Table IX. Base case analysis results.

Variable	Empagliflozin + Standard of Care	Standard of Care	Incremental
Life years per patient	20.6	14.4	6.2
QALYs per patient	10.7	8.0	2.7
Total costs per patient, yen	3,335,489	2,220,014	1,115,475
Drug costs per patient, yen	1,234,473	0	1,234,473
Event costs per patient, yen	2,101,017	2,220,014	−118,997
ICER, yen/QALY	—	—	415,849

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year.

time of the investigation (eg, reduction of medical service fees for PCI), and differences in the definitions used for the data collection. Furthermore, differences in target populations used for analyses might underlie the differences in medical cost estimates. In this report, we estimated the medical cost for a population with T2DM based on the inclusion/exclusion criteria of the EMPA-REG OUTCOME trial; for example, those patients who have a history of CV disease and who did not have cancer or end-stage renal failure records at baseline. Conversely, in the previous report,[35] those costs were analyzed without any limits placed on the population. Nevertheless, even if some medical cost discrepancies were observed compared with previous reports, the ICER of empagliflozin reported here was derived by using a more conservative analysis as the medical costs we applied were lower than those used in previous reports.

A cost-effectiveness analysis of empagliflozin using the same modeling framework as the one used in this analysis has been reported based on the health care systems in the United States, the United Kingdom, Greece, and Italy.[11–14] Empagliflozin was concluded

Table X. Results of sensitivity analysis.

Variable	Incremental Life Years Per Patient	Incremental QALYs Per Patient	Incremental Total Costs Per Patient (yen)	ICER (yen/QALY)
Base case	6.2	2.7	1,115,475	415,849
The effect of empagliflozin as 0				
Nonfatal MI	6.0	2.6	1,221,352	472,069
Nonfatal stroke	6.3	2.7	1,107,703	409,196
Hospitalization for UA	6.2	2.7	1,125,859	419,920
Hospitalization for HF	6.1	2.6	1,126,375	427,022
Transient ischemic attack	6.2	2.7	1,123,215	420,156
Revascularization	6.2	2.7	1,096,915	409,037
Progression of albuminuria	4.0	1.7	744,642	429,802
Composite renal outcome	5.0	2.2	1,204,914	543,184
CV death	1.5	0.7	805,844	1,214,694
The time horizon at 5 y	0.1	0.1	214,510	2,338,450
The time horizon at 10 y	0.8	0.5	333,938	725,255
Disutility of dialysis	6.2	2.7	1,115,475	415,557

CV = cardiovascular; HF = heart failure; ICER = incremental cost-effectiveness ratio; MI = myocardial infarction; QALY = quality-adjusted life year; UA = unstable angina.

to be cost-effective in all studies. The ICER of empagliflozin plus SoC compared with SoC alone was $24,604[11] (2,731,044 yen/QALY [$1 = 111 yen]), £4083/QALY[12] (529,035 yen/QALY [£1 = 145 yen]), €4811/QALY[13] (625,430 yen/QALY [€1 = 130 yen]), and €4633/QALY[14] (602,290 yen/QALY [€1 = 130 yen]), respectively. The cost-effectiveness of empagliflozin has been established in the United States, the United Kingdom, Greece, and Italy based on an analysis of the overall population of the EMPA-REG OUTCOME trial; in contrast, we used the Asian subpopulation. Although several differences were identified (eg, drug cost of empagliflozin, discount rate for analysis, degree of effect of empagliflozin on CV death), the overall cost-effectiveness of empagliflozin was consistent between the United States, the United Kingdom, Greece, Italy, and Japan.

Because this model analysis is based on EMPA-REG OUTCOME trial data, we needed to consider several limitations for our interpretation. First, the incidence of potential events was estimated over an entire lifetime beyond the follow-up period of the EMPA-REG OUTCOME trial. Therefore, uncertainty would remain in terms of the validation of long-term risk estimation beyond that period. This scenario may possibly cause a large change in the results of the long-term risk estimation depending on the distribution function used in this analysis. To minimize such a dissociation in the long-term risk estimation, sensitivity and scenario analyses were performed. Because we assumed that empagliflozin will greatly influence the results of a

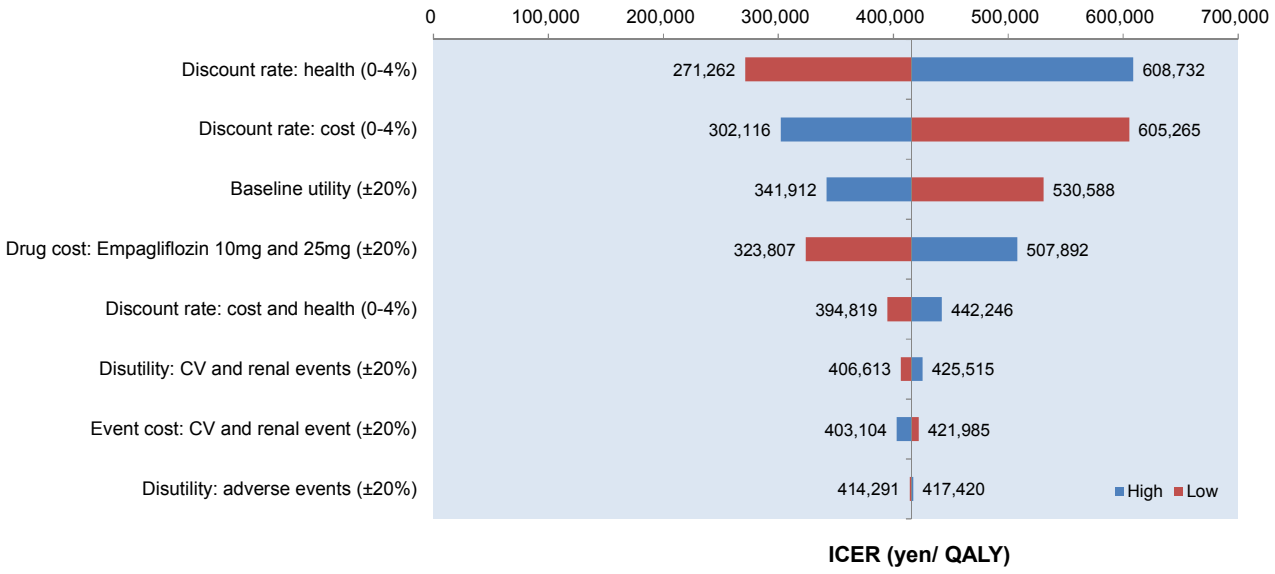


Figure 3. One-way sensitivity analysis. The base case value is shown as the central vertical line. The blue bar represents the result when the parameter was changed to high value (eg, the parameter change to +20%), and the red bar represents the result when it was changed to low value (eg, the parameter change to −20%). The discount rate exerted the greatest effect on the results of the analysis. According to the one-way sensitivity analysis using data from overseas studies, including the baseline utility and disutility, the results ranged from 341,912 to 530,588 yen/quality-adjusted life year (QALY) and from 406,613 to 425,515 yen/QALY, respectively. CV = cardiovascular.

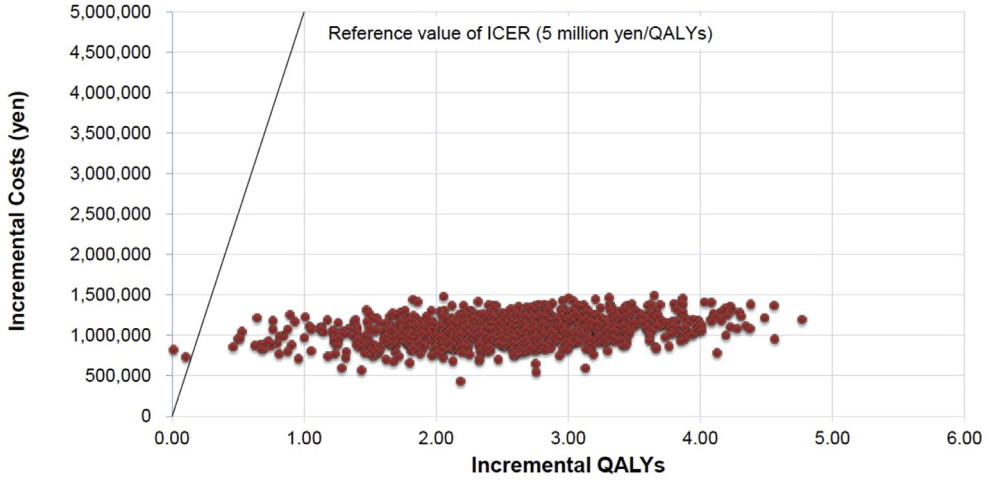


Figure 4. Probabilistic sensitivity analysis. The line indicates the reference value of the incremental cost-effectiveness ratio (ICER) (5 million yen/quality-adjusted life year [QALY]) in Japan. Probability of being cost-effective (ICER <5 million yen) exceeded 99% in the empagliflozin plus standard of care group compared with the standard of care alone group.

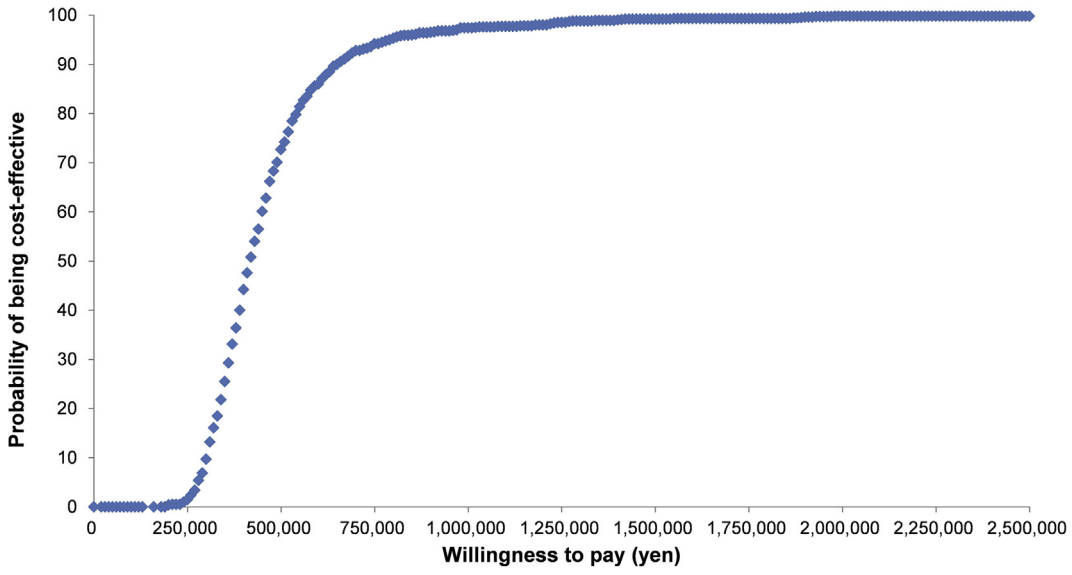


Figure 5. Cost-effectiveness acceptability curve. The willingness-to-pay was ~420,000 yen; the probability of being cost-effective (incremental cost-effectiveness ratio <5 million yen) of empagliflozin plus standard of care was considered adequate (exceeds 50%).

long-term estimation, we also assumed the clinical effect to be 0. We also restricted the time horizon to 5 and 10 years. As a result, the ICER for empagliflozin was sufficiently lower than the ICER reference value. Taken together, those results suggest that the potential dissociation for long-term estimation minimally influenced the outcomes of our analysis.

Second, the medical costs of the potential events were estimated with data from ~19% of the DPC hospitals (as stated earlier), suggesting that cost estimation would be highly generalizable for DPC hospitals. However, the medical costs may differ for nationwide hospitals (ie, including non-DPC hospitals). The medical costs would be underestimated due to a higher incentive to provide medical services more efficiently in the comprehensive payment systems of DPC hospitals rather than general hospitals. However, the underestimation of treatment costs for potential events would influence the cost-effectiveness of empagliflozin in a conservative manner; thus, the results of this analysis would not markedly change due to the underestimation of event medical cost.

Lastly, although the purpose of the current analysis was to assess the cost-effectiveness of empagliflozin based on the health care systems in Japan, we could not use Japanese utility values because they were not available in the previous report. In sensitivity and scenario analyses, we evaluated the influence of the baseline utility, disutility, and clinical effect of empagliflozin to be 0 on our conclusion. The ICER values of empagliflozin in all analyses were lower than the reference ICER values mentioned earlier. Therefore, the impact of using non- Japanese utility values on our conclusion is limited.

Taken together, these limitations would have minimal impact on our interpretation of the results.

CONCLUSIONS

We conducted a cost-effective analysis of empagliflozin using a patient-level simulation based on the Asian

subpopulation data, including Japanese patients in the EMPA-REG OUTCOME trial and the medical costs for diabetes and diabetes-related complications in Japan. In this analysis, treatment with empagliflozin plus SoC led to improved survival and higher QALYs than SoC alone. The ICER of empagliflozin was lower compared with the reference values of ICER. Empagliflozin would be a highly cost-effective option in Japan for treating patients with T2DM and established CV disease.

DISCLOSURES

Dr. Kaku has received fees for an advisory role from Sanwa Kagaku Kenkyusho, Kissei Pharmaceutical, Novo Nordisk Pharma, Takeda Pharmaceutical Company; honoraria or fees for promotional materials from Astellas Pharma, AstraZeneca, Daiichi Sankyo, MSD, Ono-Pharmaceutical, Novo Nordisk Pharma, Boehringer Ingelheim Japan, Taisho Toyama Pharmaceutical, Takeda Pharmaceutical Company, Mitsubishi Tanabe Pharma; and a scholarship or donation from Boehringer Ingelheim Japan, Taisho Toyama Pharmaceutical, and Mitsubishi Tanabe Pharma. Dr. Haneda has received honoraria from Astellas Pharma, Taisho Toyama Pharmaceutical, Mitsubishi Tanabe Pharma, Boehringer Ingelheim, Taisho, Kowa, Ono-Pharmaceutical, MSD, Novartis, Novo Nordisk Pharma, Sanofi, Daiichi Sankyo, Eli Lilly, Kyowa Kirin, Shionogi, Johnson & Johnson, Otsuka, and Kissei Pharmaceutical. Dr. Sakamaki has received honoraria from Abbott Medical Japan, Boehringer Ingelheim Japan, Chugai Pharmaceutical, Daiichi Sankyo Espha, Edwards Lifesciences, Eli Lilly, Japan Tissue Engineering, Japan Tobacco, Kyowa Kirin, Medtronic Japan, Meiji Seika Pharma, Mochida Pharmaceutical, Nippon Kayaku, Novartis Pharma, Novo Nordisk Pharma, Sandoz Japan, Sawai Pharmaceutical, Symbio Pharmaceuticals, and Taiho Pharmaceutical. Dr. Yasui, Shibahara, Hayashi, and Dr. Okamura are employees of Boehringer Ingelheim Co Ltd. Chin and Dr. Hirase are employees of Eli Lilly Japan K.K. Murata is an employee of CRECON Medical Assessment Inc and a consultant for Nippon Boehringer Ingelheim Co Ltd. Ustyugova and Kaspers are employees of Boehringer Ingelheim International GmbH. Dr. Kansal is an employee of Evidera and a consultant for Boehringer Ingelheim Co Ltd. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

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Dr. Yasui, Chin, Dr. Hirase, and Dr. Okamura drafted the concept of this research. Dr. Kansal created the simulation model. Murata performed all analyses using the model and drafted the manuscript. All authors participated in the interpretation of study results and in the drafting, critical revision, and approval of the final version of the manuscript.

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SUPPLEMENTAL MATERIAL

Model Selection

Several parameterization models for estimating clinical event rates were first tested based on statistical goodness of fit. The Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) measures were used to assess relative model fit. Parametric fits using the Exponential, Weibull, Log-normal, Log-logistic, Generalized Gamma, and Gompertz distributions were computed for each cardiovascular (CV) and renal outcome. The distribution giving the smallest AIC/BIC value was generally selected as the best-fitting model.

The model selections were performed using only treatment as a predictor. Therefore, the AIC and BIC values presented herein were based on equations without other predictors. Once the distributions were selected, additional predictors were then tested via parametric survival regression. AIC and BIC were not estimated for the parametric survival regression with predictors. Including predictors in the functions is not expected to change the decision of the distribution selections.

For virtually all event types, the multiple fits considered (and in some cases, all) provided good fits, with relatively little distinction between the AIC and BIC values for the various fits. Given that, the primary statistical form for each event was chosen based not only on the quality of the fit, but also on the plausibility of long-term projections, and the simplicity of the fitting form. A summary of the fits (AIC and BIC values) is provided below followed by a more detailed description of the individual event types.

Table 1. Fit Quality (AIC and BIC) for Each Event Type for All Statistical Forms Tested.

	Non-fatal MI		Non-fatal Stroke		UA hospitalization	
Distribution	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Weibull	297.6	307.2	360.6	370.1	267.8	277.4
Log-normal	299.3	308.9	359.1	368.7	268.1	277.7
Log-logistic	297.7	307.2	360.5	370.1	267.8	277.4
Exponential	295.7	300.5	358.7	363.5	267.4	272.2
Generalized gamma	299.5	313.9	362.7	377.0	269.8	284.2
Gompertz	297.0	306.5	359.8	369.4	268.8	278.4
	HF hospitalization		**Transient ischemic attack**		**Revascularization**	
Distribution	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Weibull	229.8	239.3	34.7	44.3	540.4	550.0
Log-normal	229.8	239.4	34.6	44.2	541.6	551.1
Log-logistic	229.7	239.3	34.7	44.3	540.5	550.1
Exponential	228.7	233.5	34.9	39.7	538.9	543.7
Generalized gamma	231.7	246.0	36.8	51.1	542.4	556.7
Gompertz	228.8	238.4	32.5	42.1	540.2	549.8
	Albuminuria progression		**Composite renal outcome**		**CV death**	
Distribution	**AIC**	**BIC**	**AIC**	**BIC**	**AIC**	**BIC**
Weibull	1897.9	1907.1	239.0	248.6	216.7	226.3
Log-normal	1926.8	1936.0	239.6	249.2	216.6	226.1
Log-logistic	1912.3	1921.5	239.0	248.6	216.7	226.3
Exponential	1912.0	1916.6	237.5	242.3	219.4	224.2
Generalized gamma	1888.9	1902.7	241.0	255.3	218.7	233.1
Gompertz	1893.2	1902.4	238.8	248.3	217.5	227.1

AIC:Akaike's Information Criteria, BIC: Bayesian Information Criterion, CV: cardiovascular, HF: heart failure, MI:myocardial infarction, UA: unstable angina

Comparison of Statistical Fits to Observed Data

The parametric fits were visually inspected to evaluate clinical plausibility of the projections over the short-term trial duration and the long-term life-time time-horizon. Plots showing the fraction of patients remaining event-free (y-axis) over time (years; x-axis) with the different fits overlaid on the observed KM curves are provided below, along with a rationale for the selected distribution.

Non-fatal MI

Over the observed trial period, all fits provided good agreement with the observed data. The distributions were bracketed by Gompertz (high rates of non-fatal MI) and log-normal (implausibly high values of >80% event-free at 40 years) distributions. The Exponential distribution was selected as it had the best AIC/BIC values.

Non-fatal Stroke

Over the observed trial period, all fits provided good agreement with the observed data. Over a longer time horizon, the fits separate slightly, but all predict >50% of the population to remain event-free after 40 years. The Gompertz and Log-Normal distributions plateau at the highest values and were considered to predict too few events at longer times, with the remaining four distributions clustered in their predictions. The Weibull distribution was selected as it is a mid-point among these.

Hospitalization for UA

Over the observed trial period, all fits provided good agreement with the observed data. There was a fairly low rate of UA hospitalization with little curvature in the observed event-free survival curve. The Exponential distribution was selected as it had the best AIC/BIC values.

Hospitalization for HF

Over the observed trial period, all fits provided good agreement with the observed data. Over a longer time horizon, Gompertz distribution predicts a low number of events, with nearly 100% of the population remaining event free at 50 years. Exponential distribution had the highest rate of events. Of the four remaining distributions, the Weibull distribution was selected as it is a mid-point among gompertz and exponential distributions.

Transient Ischemic Attack

Over the observed trial period, all fits provided good agreement with the observed data, which showed very few events. The Exponential distribution was selected as it had the simplest form and the best AIC/BIC values.

Revascularization

Over the observed trial period, all fits provided good agreement with the observed data, with the spread between all curves starting at 4 years and remaining relatively tightly spread through 10 years. The Exponential distribution was selected as it had the best AIC/BIC values.

Progression of Albuminuria

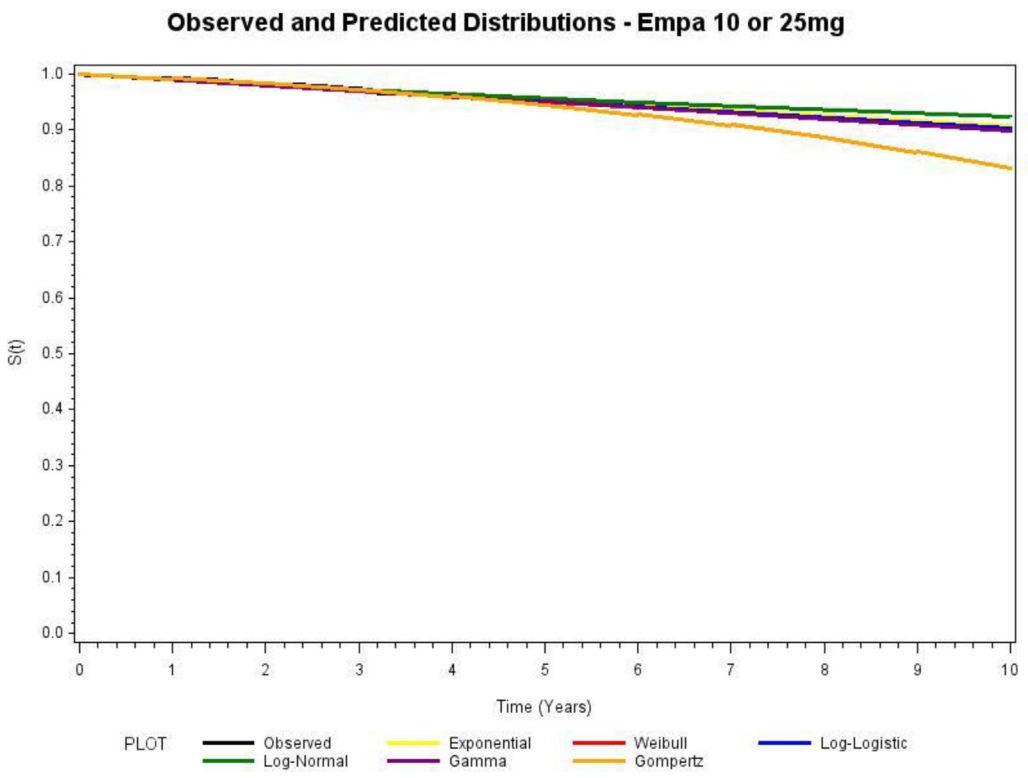
Over the observed trial period, all fits provided good agreement with the observed data up to 4 years. Predicted values diverged in the tail due to the small number at risk. Weibull distribution was selected as the mid-point among the distributions to avoid overfitting the tail of the KM curve, with the next best AIC and BIC after Gamma and Gompertz distributions.

Composite Renal Outcome

Over the observed trial period, all fits provided good agreement with the observed data. Over a longer time horizon, the Gompertz distribution curve diverges the most. Exponential distribution was selected as it had the simplest form and lowest AIC/BIC.

CV Death

Over the observed trial period, all fits provided good agreement with the observed data. However, the fits separate over a longer time horizon, with the Gompertz and Gamma distributions predicting nearly 100% mortality due to CV death within 40 years, while the Exponential distribution predicts <20%. Of the remaining 3 fits, the Weibull distribution was selected as it is a mid-point among all distributions.



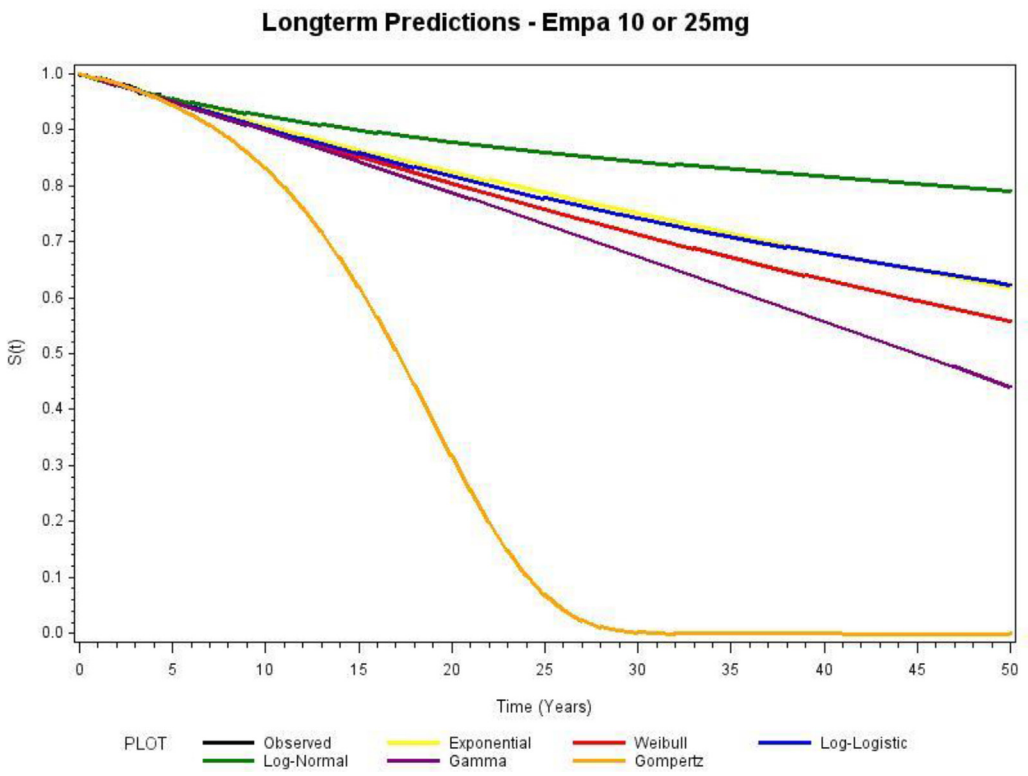


Figure 1. Comparison of Statistical Fits to Observed Data for Non-fatal MI.

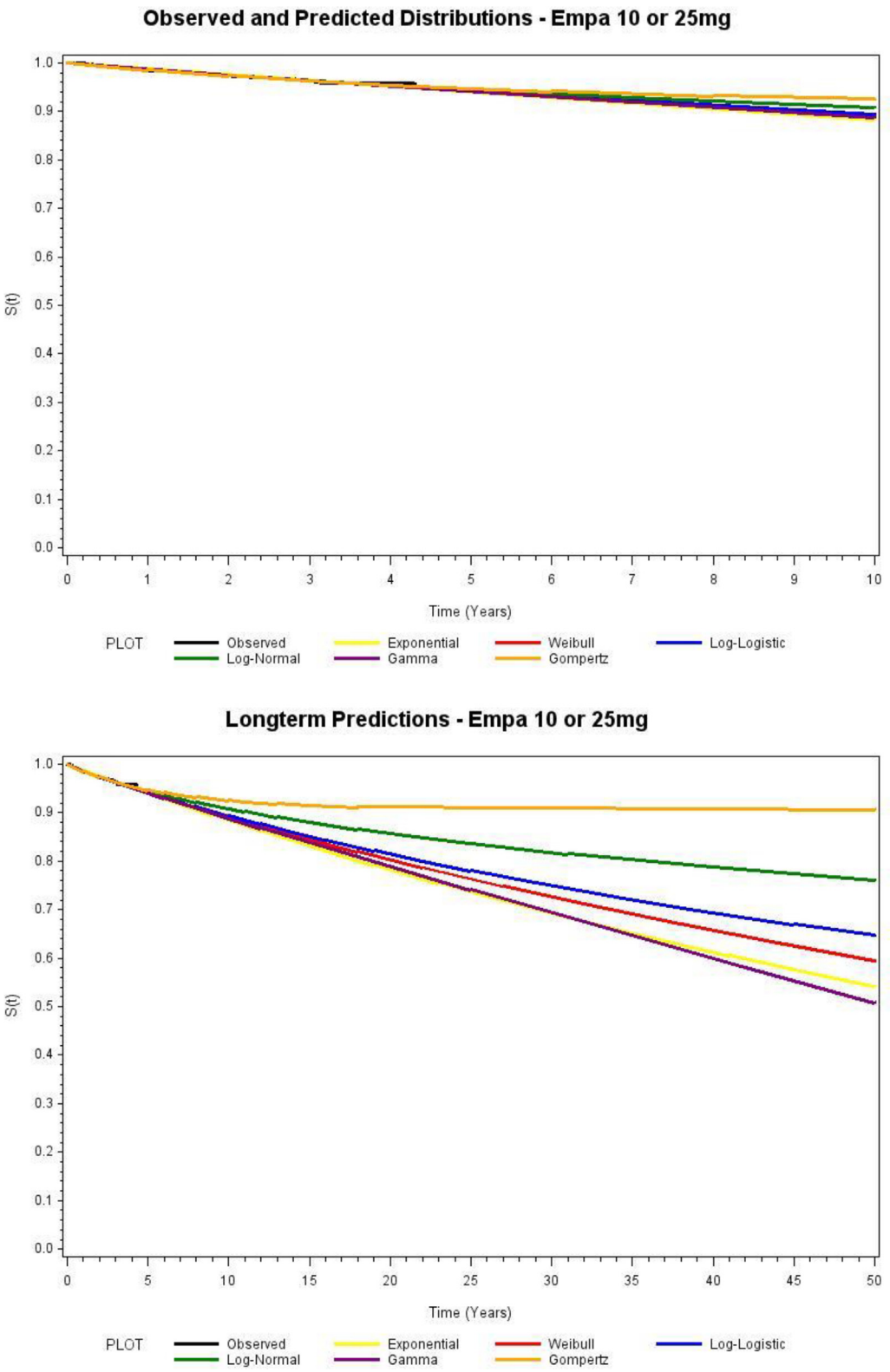


Figure 2. Comparison of Statistical Fits to Observed Data for Non-fatal Stroke.

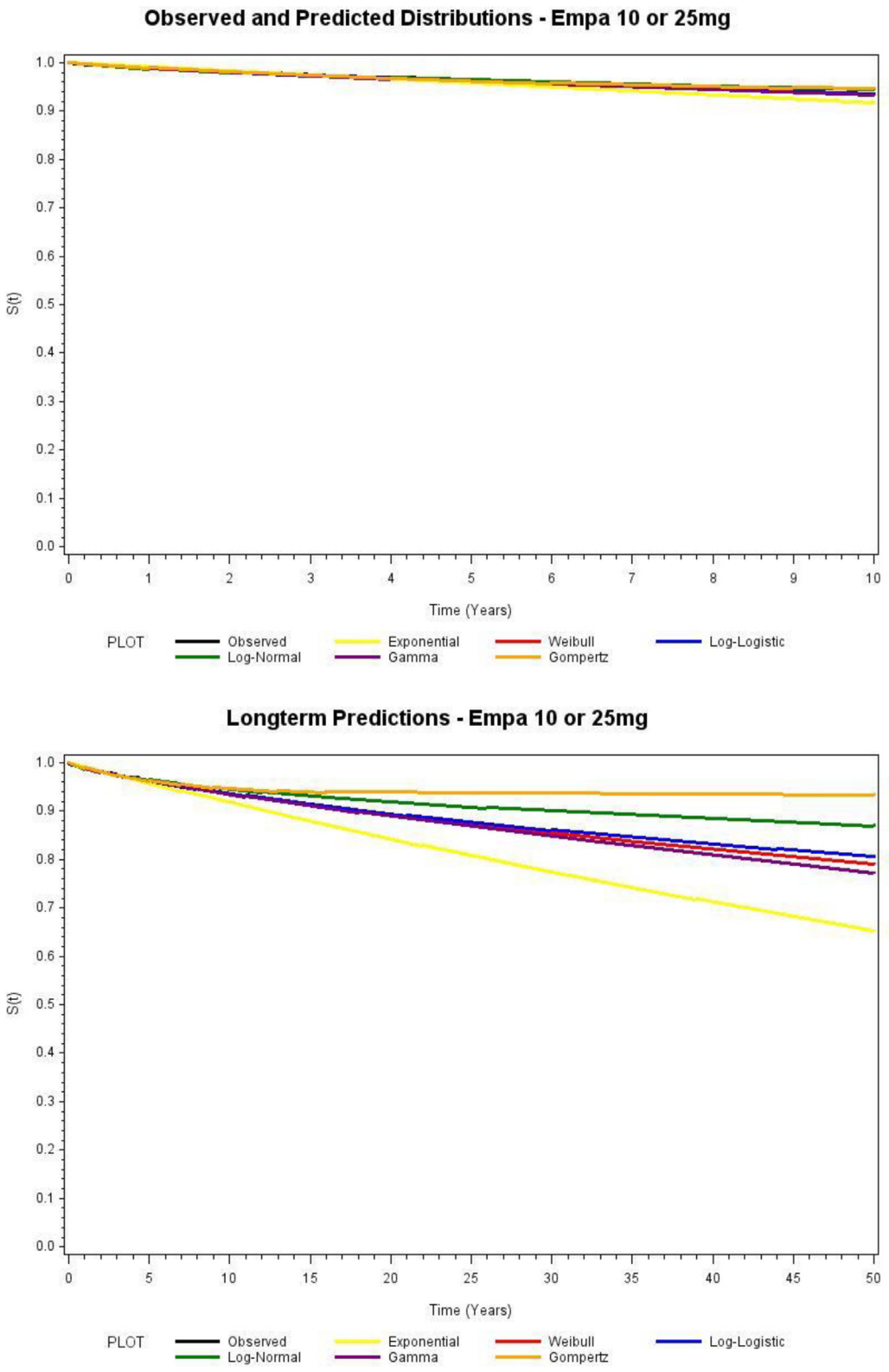
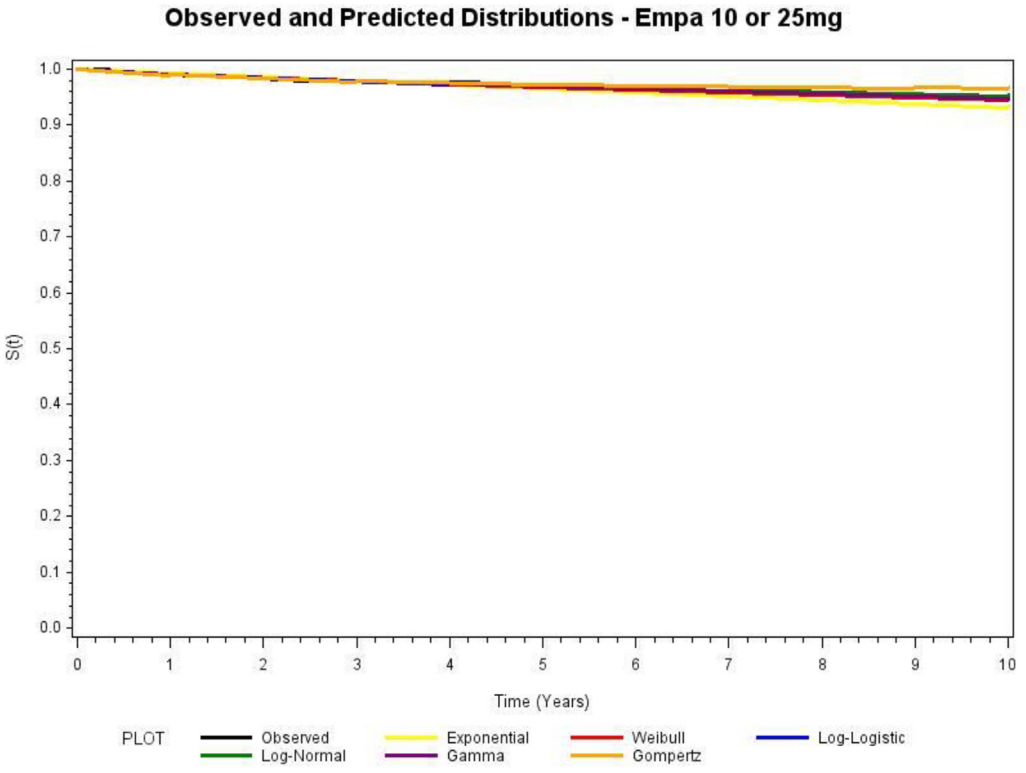


Figure 3. Comparison of Statistical Fits to Observed Data for UA Hospitalization.



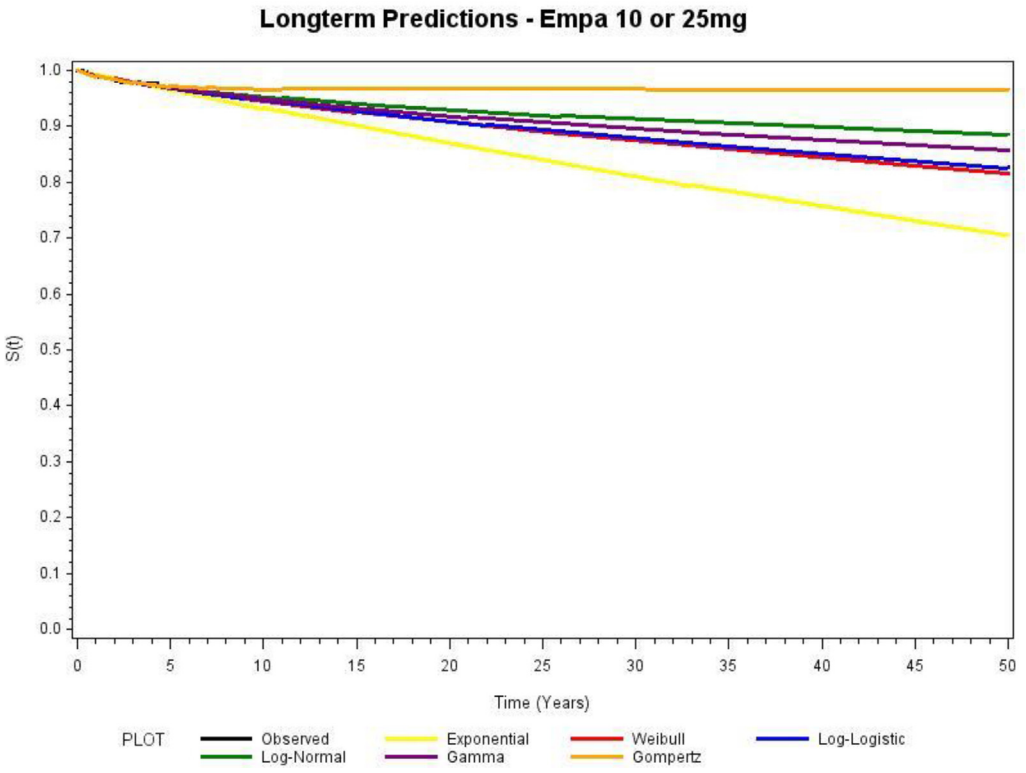


Figure 4. Comparison of Statistical Fits to Observed Data for HF Hospitalization.

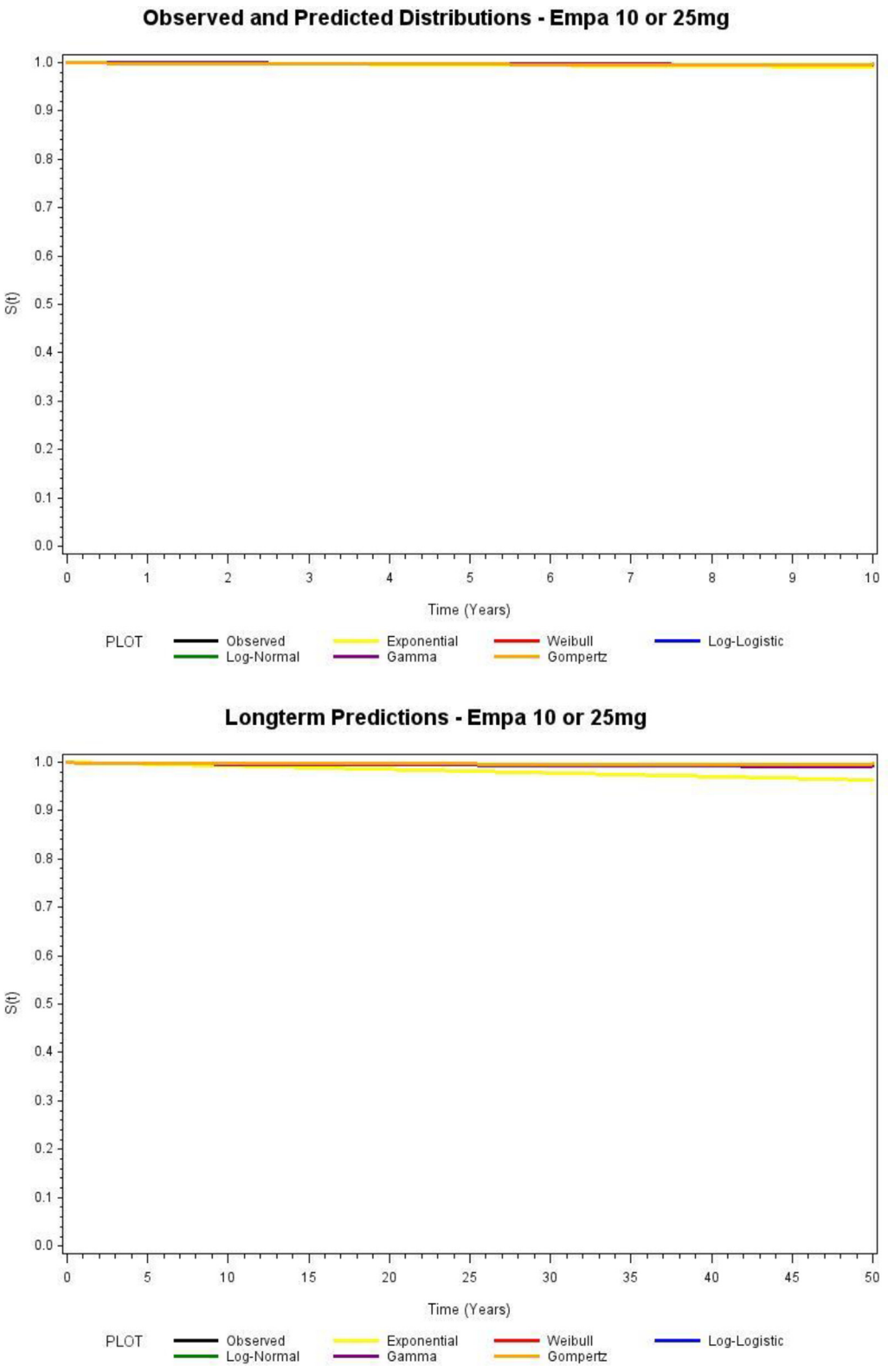
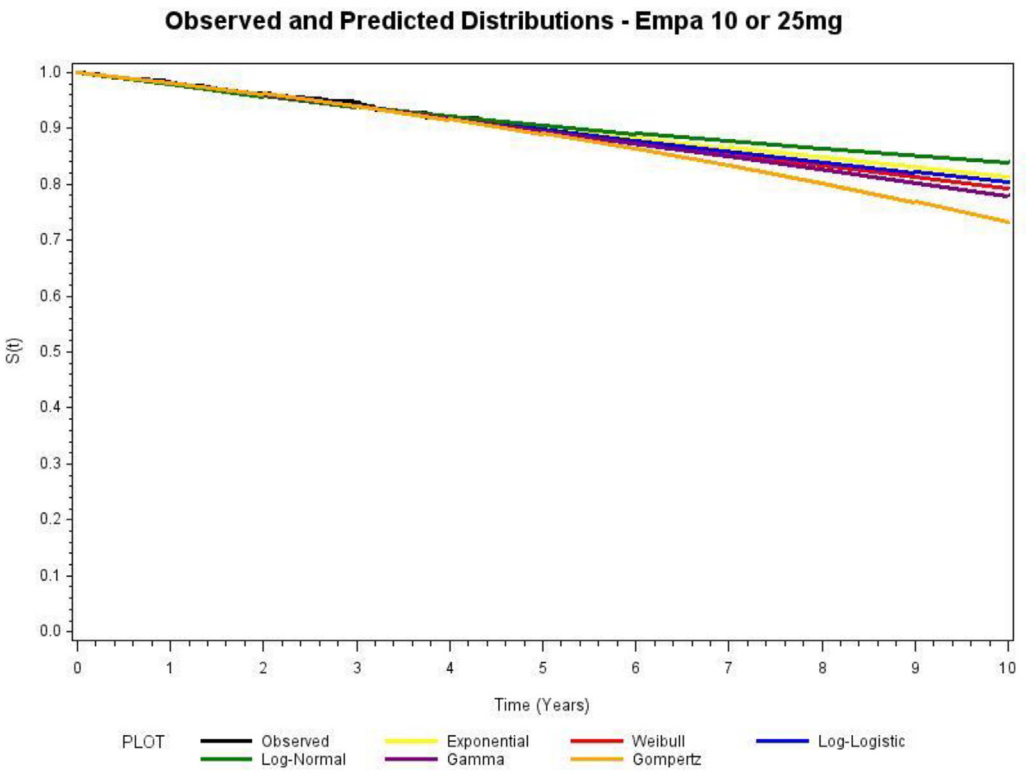


Figure 5. Comparison of Statistical Fits to Observed Data for Transient Ischemic Attack.



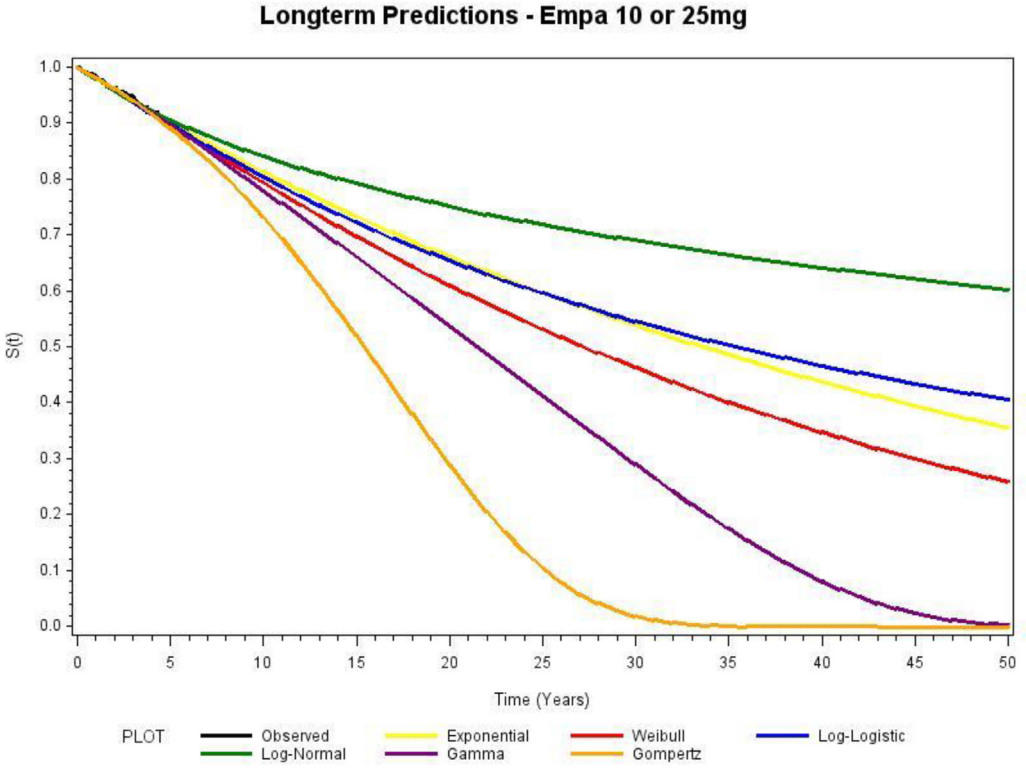
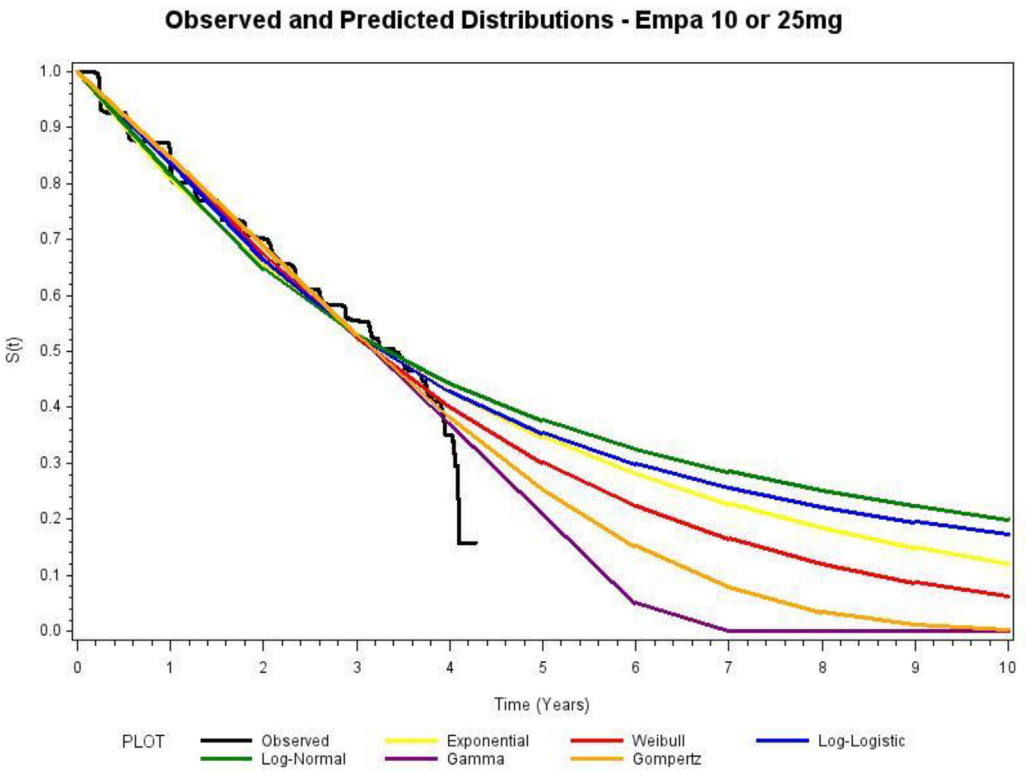


Figure 6. Comparison of Statistical Fits to Observed Data for Revascularization.



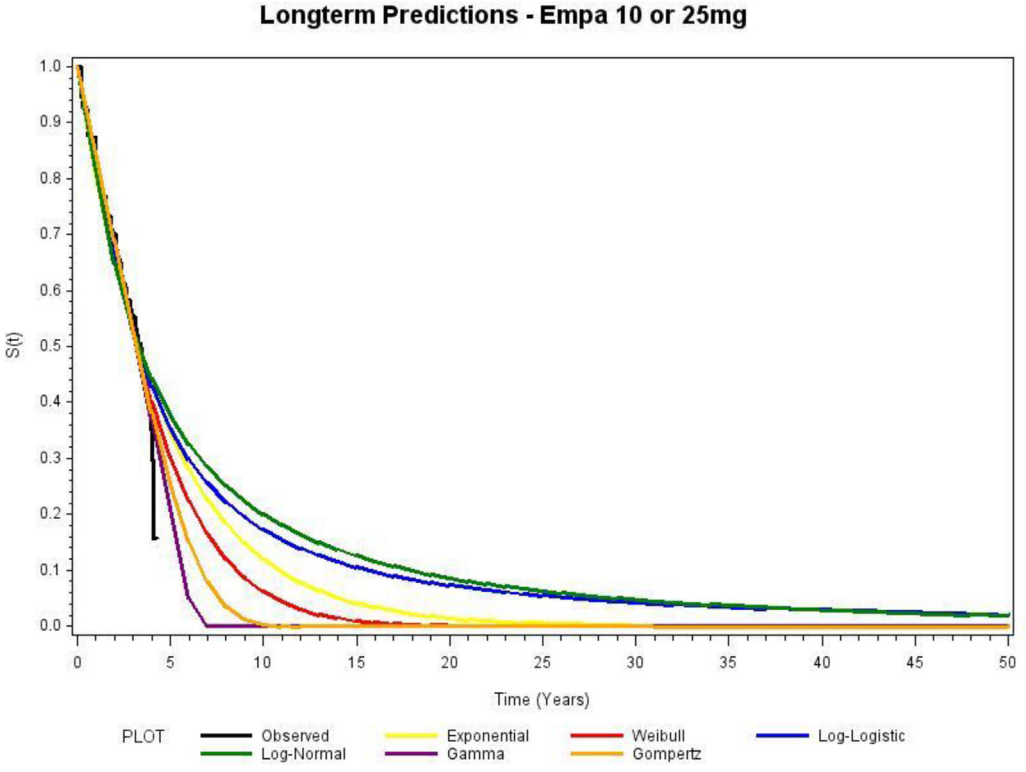
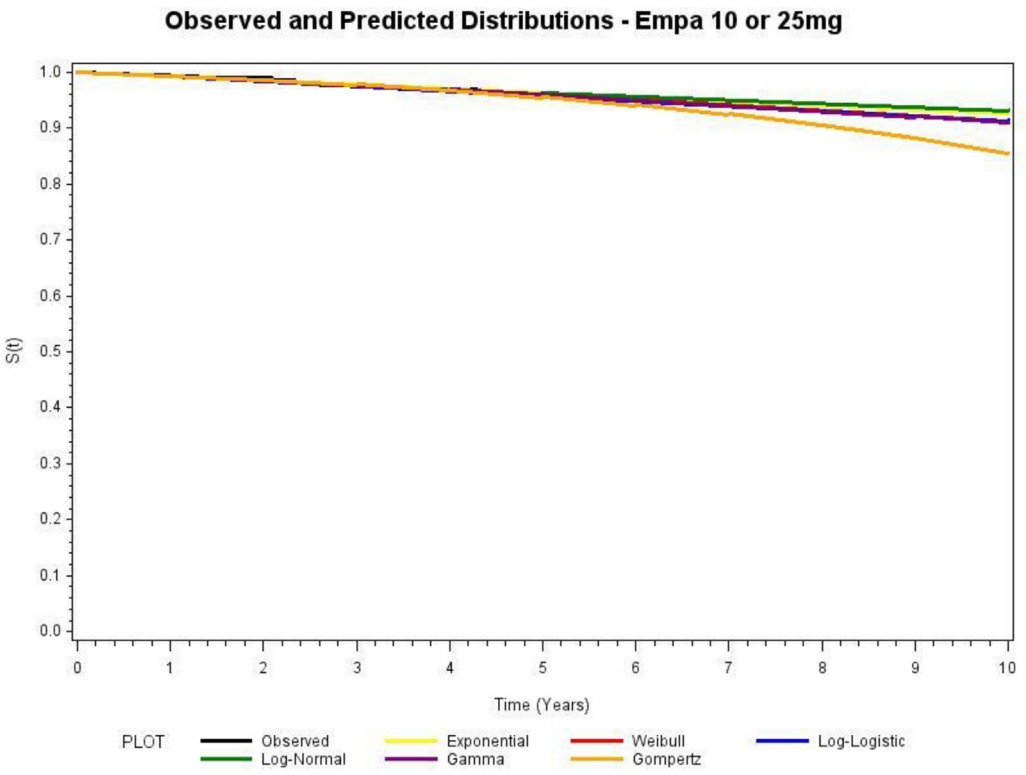


Figure 7. Comparison of Statistical Fits to Observed Data for Progression of Albuminuria.



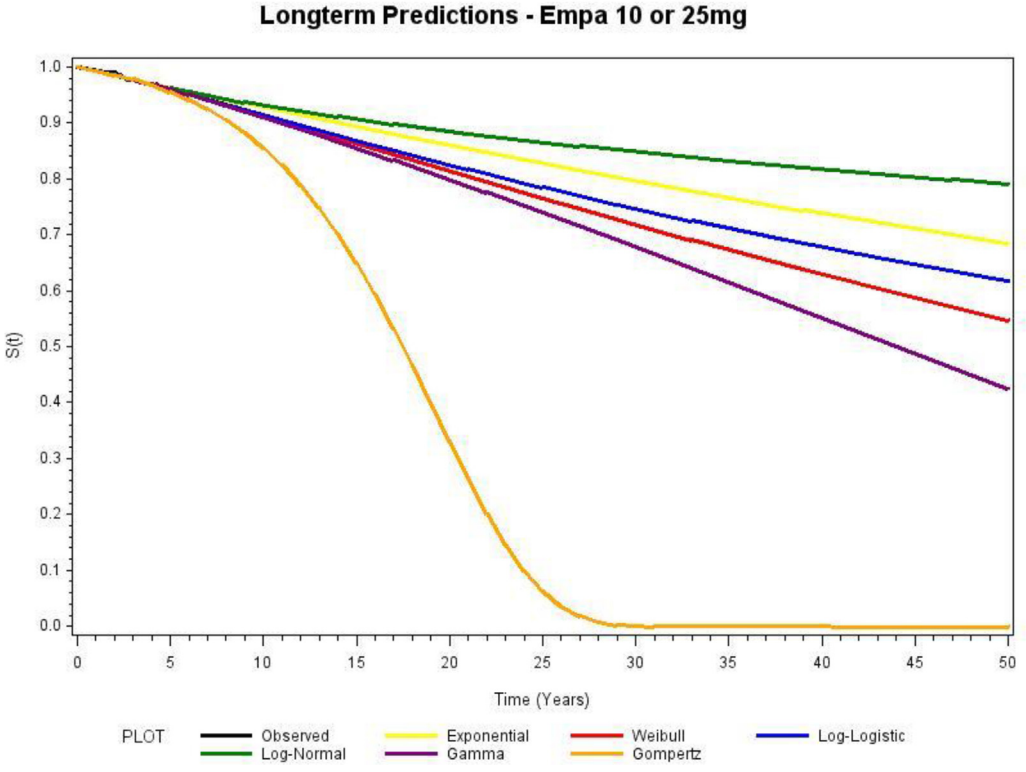


Figure 8. Comparison of Statistical Fits to Observed Data for Composite Renal Outcome.

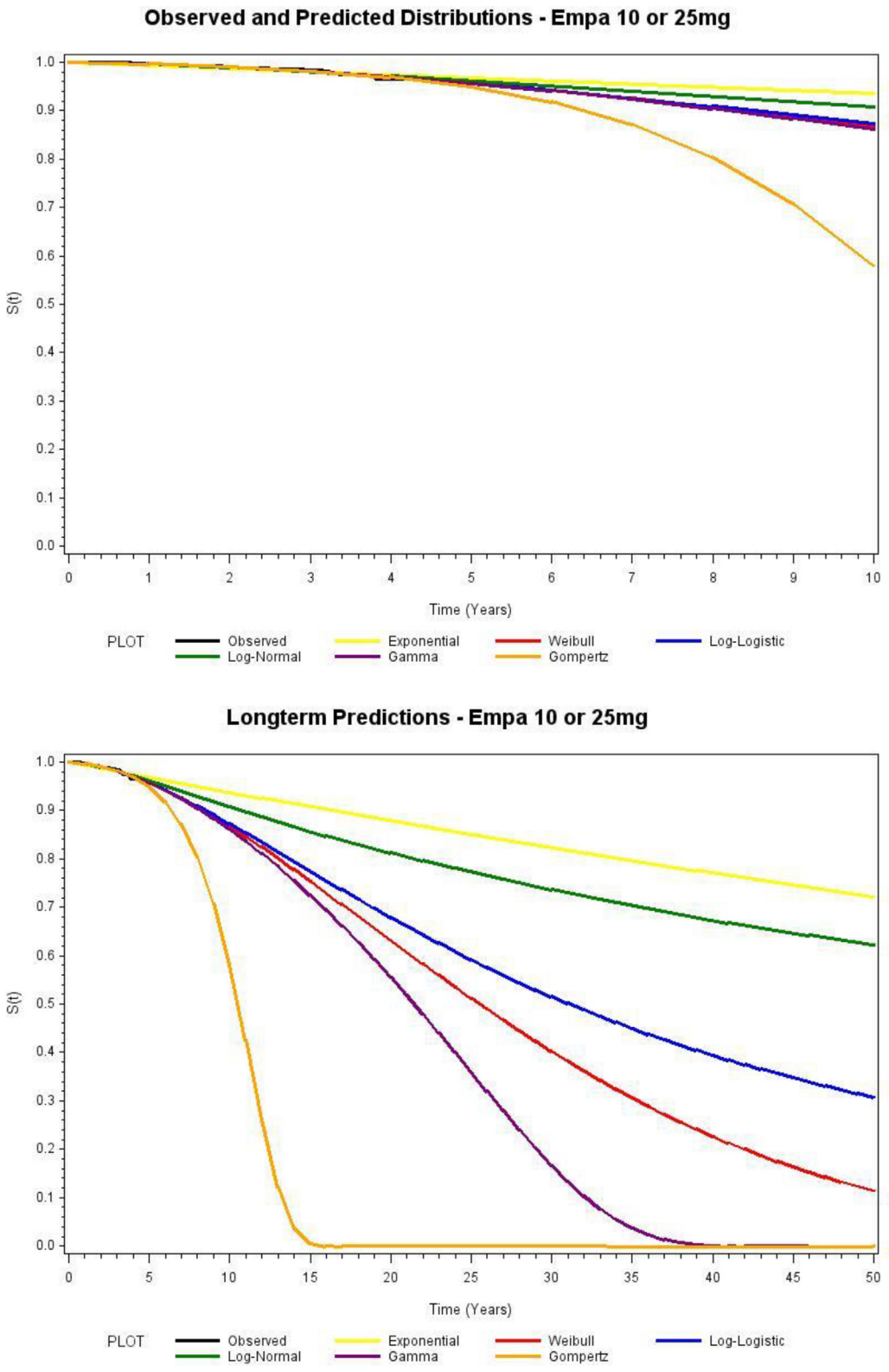


Figure 9. Comparison of Statistical Fits to Observed Data for CV Death.