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ORIGINAL ARTICLE

Modeling effects of SGLT-2 inhibitor dapagliflozin treatment versus standard diabetes therapy on cardiovascular and microvascular outcomes

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Aims: Dapagliflozin, a sodium-glucose cotransporter 2 (SGLT-2) inhibitor, has been shown to lower glycated hemoglobin (HbA1c), weight, blood pressure and serum uric acid in clinical trials. Plasma lipids were also evaluated as exploratory variables. The goal of this study was to estimate the long-term cardiovascular (CV) and microvascular outcomes of dapagliflozin added to the standard of care (SOC) versus SOC using simulation methodology.

Methods: The Archimedes Model, a validated model of human physiology, diseases and healthcare systems, was used to model a type 2 diabetes mellitus (T2DM) population derived from National Health and Nutrition Examination Survey (NHANES) with HbA1c 7–10%, taking a single oral antidiabetic agent [metformin, sulfonylureas SU or thiazolidinedione (TZD)] at the beginning of the trial. A 20-year trial was simulated comparing dapagliflozin 10 mg, given in addition to SOC, with SOC alone. SOC was based on American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) 2012 guidelines and included diet, metformin, SU, TZD, dipeptidyl peptidase-4 (DPP-4), glucagon-like peptide-1 (GLP-1), and insulin therapies, with usage levels reflective of those in NHANES. Dapagliflozin effects were derived from phase 3 clinical trial results. End points included CV and microvascular outcomes.

Results: Over a 20-year period, patients on dapagliflozin were projected to experience relative reductions in the incidence of myocardial infarction (MI), stroke, CV death, and all-cause death of 13.8, 9.1, 9.6 and 5.0%, respectively, and relative reductions in the incidence of end-stage renal disease (ESRD), foot amputation, and diabetic retinopathy of 18.7, 13.0 and 9.8%, respectively, when compared with SOC.

Conclusions: On the basis of simulation results, adding dapagliflozin to currently available treatment options is projected to further decrease the CV and microvascular complications associated with T2DM.

Keywords: antidiabetic drug, diabetes mellitus, renal glucose handling, SGLT2 inhibitor, type 2 diabetes, weight loss therapy

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Type 2 diabetes mellitus (T2DM) is a chronic disease that affects approximately 312 million people worldwide [1]. As a significant proportion of patients with diabetes will die of or experience cardiovascular (CV) events, a particular emphasis is placed on CV risk factor management among patients with T2DM [2]. Despite recent significant advances in new treatment targets and approved treatment options, achieving and maintaining treatment goals in T2DM remain challenging [3]. This difficulty is highlighted in the latest American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) 2012 guidelines, which stress the importance of an individualized treatment approach [4]. Recent data from the United States (US) National Health and Nutrition Examination Survey (NHANES) survey indicate that significant progress has been made in advancing the goal of glycaemic control as well as improving the control of other CV risk factors such as blood pressure (BP) and lipids. However, there has been no progress in managing obesity as a feature of T2DM. Indeed, the proportion of US patients with T2DM at simultaneous control of these risk factors remains in the single digits [5,6]. New pathways and mechanisms of action are continually being investigated to tighten control and achieve larger reductions in CV and microvascular outcomes.

Dapagliflozin is a new orally active sodium-glucose cotransporter 2 (SGLT-2) inhibitor under development by Bristol-Myers Squibb (BMS) and AstraZeneca (AZ). Dapagliflozin's mechanism of action (MOA) is different from and complementary to the mechanisms of currently available antidiabetic medicines, resulting in the direct, and insulin-independent, elimination of glucose by the kidney. Glucosuria is associated with plasma glucose reductions, as well as caloric loss,

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which lead to weight reductions and mild osmotic diuresis which leads to BP reductions. Furthermore, because SGLT-2 is almost exclusively expressed in the kidney, the highly selective nature of dapagliflozin minimizes the risk of off-target (i.e. non-kidney) effects. As such, dapagliflozin offers an important additional strategy for improving glycaemic control in patients with T2DM.

In randomized, controlled clinical trial [7–12], dapagliflozin use resulted in improved glycaemic control along with reduced BP, weight and serum uric acid (SUA). Dapagliflozin also had a modest effect on lipids, which were evaluated as exploratory variables. Although glucose, BP, weight and lipids are all establishedCV risk factors, the role of SUA is still being understood. The association of SUA with metabolic risk factors for CV disease is well established [13–16]. However, its independence from traditional CV disease risk factors and its causal role in CV disease are still under discussion [17,18]. Although studies have shown mixed results regarding whether SUA is an independent risk factor for CV disease and all-cause mortality [19–22], there is evidence to suggest that lowering SUA levels is associated with an improvement in these outcomes [23–27]. A CV meta-analysis evaluating up to 2.5-year data across the Phase 2b/3 programme suggested that dapagliflozin is not associated with an increase in CV risk relative to comparator (predominantly placebo) [Hazard ratio: 0.82; 95% confidence interval (CI) 0.58, 1.15 for CV death, MI, stroke and hospitalization for unstable angina].

The primary aim of this work is to model the impact on long-term CV and microvascular outcomes of dapagliflozin (10-mg dose) available as part of the standard treatment options for patients with T2DM compared with the standard of care (SOC) today. The population of interest comprises patients with T2DM who are on oral antidiabetic monotherapy and have glycated hemoglobin (HbA1c) > 7% (i.e. uncontrolled on monotherapy). We evaluate the potential effects of adding dapagliflozin to established treatments in this population using the Archimedes Model.

Methods

The Archimedes Model

The Archimedes Model is a validated, clinically detailed simulation model of human physiology, disease progression and healthcare delivery. At its core, the Model is a set of algebraic and differential equations that represent physiological pathways of diseases and their complications [28]. The Model has been validated against more than 50 clinical trials, including several pertinent to diabetes treatment and management [29]. As a result, it has been used extensively to model novel treatments and simulate clinical trials in the cardiometabolic space in order to estimate the impact of various diabetes treatment strategies in reducing CV disease [30,31].

In this work, we extended the Archimedes Model to include an SUA pathway that associates changes in SUA with reductions in CV disease and death rates. We evaluated the independent effect of SUA on five outcomes: myocardial infarction (MI) incidence, and stroke incidence, coronary heart disease (CHD) death, stroke death, and all-cause mortality for male and female populations diagnosed with diabetes. This modeling is discussed in detail in the Appendix S1, Supporting Information.

Study Population

We evaluated dapagliflozin as an add-on therapy in patients with T2DM uncontrolled on established DM oral monotherapy treatment [i.e. metformin, sulfonylureas (SU), or thiazolidinedione (TZD)]. We created a simulated population of 30 000 per treatment strategy by using person-specific data from the NHANES (years 1999–2008). Although this database is representative of the US population, its use in Europe-based simulations has shown that it is adequate in representing European populations with similar baseline risk and qualities of healthcare as the US [32]. It should also be noted that because the NHANES dataset used in this study is historic, some of the medication prevalence could be different from current practice. A possible consequence of this could be an overestimation of benefit from SGLT2 inhibitors due to a lower than expected usage of statins and/or glucagon-like peptide-1 (GLP-1)/dipeptidyl peptidase-4 (DPP-4) therapies. By sampling NHANES, we selected a cross section of the adult population that represents our target population and had the same distributions and correlations of risk factors, medication usage and disease histories as seen in NHANES. We included patients with T2DM aged 18–70 years who had HbA1c between 7 and 10%, estimated glomerular filtration rate (eGFR) ≥60 ml/min/1.73 m^2, and are taking metformin, SU or TZD oral antidiabetic monotherapy.

Table 1. Treatment efficacy assumptions of SGLT-2 inhibitor dapagliflozin.

Intervention	HbA1c (%) (absolute change)	SBP (mm Hg) (absolute change)	Total body weight (kg) (relative change)	Serum uric acid (relative change)	Total cholesterol (mmol/l) (relative change)	HDL-C (mmol/l) (relative change)	LDL-C (mmol/l) (relative change)	Triglycerides (mmol/l) (relative change)
Dapagliflozin-1	−0.78*	−2.39†	−2.8%*	−12.1%*	n/a	n/a	n/a	n/a
Dapagliflozin-2	−0.78*	−2.39†	−2.8%*	−12.1%*	2.12%*	6.32%*	2.48%*	−5.16%*

HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SGLT-2, sodium-glucose cotransporter 2; SBP, systolic blood pressure.
*Effect is derived from studies [7–10], restricting to patients with baseline HbA1c > 7% in [9].
†Effect is derived from studies [11,12].

Simulation Design

The simulation compared three different treatment strategies. The first represented the diabetes SOC today. Diabetes management followed the ADA/EASD 2012 guidelines and included diet, metformin, SU, TZD, DPP-4 inhibitor, GLP-1 receptor agonist and insulin treatments with usage levels reflective of those seen in NHANES. BP management was modeled based on JNC-7 guidelines and lipid management on National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines. The other two treatment strategies added dapagliflozin to the SOC T2DM treatment options.

We modeled two variants of dapagliflozin. The first, dapagliflozin-1, included the glucose-, BP-, weight- and SUA-lowering effects associated with dapagliflozin. The second, dapagliflozin-2, included these effects plus effects on lipids. Because we aimed to evaluate dapagliflozin as an add-on therapy to established T2DM monotherapy treatments, our efficacy assumptions (Table 1) were based on pooled data from phase III clinical trials that evaluated dapagliflozin as an add-on treatment to metformin, SU and TZD, including four studies that assessed HbA1c, weight, SUA and the lipid panel [7–10]. Assumptions for BP change were based on results from two add-ons to usual care studies that assessed systolic BP(SBP) as a key secondary end point [11,12].

In all treatment strategies the trial protocol began with an initial visit at the start of the simulated trial. Patients included in the study were uncontrolled on T2DM monotherapy treatment. In the SOC arm, patients were prescribed second-line SOC diabetes treatments. In the dapagliflozin arms, the patients were prescribed dapagliflozin. In all arms, a follow-up visit was scheduled in 3 months. At this visit and with subsequent follow-up care additional treatments were prescribed to patients with HbA1c > 7.0% (uncontrolled) according to the 2012 ADA/EASD guidelines. Follow-up visits were scheduled every 3 months if uncontrolled and every 6 months if controlled.

Twenty years were simulated for all three treatment strategies, with events recorded as they occurred and reported annually. We considered CV and microvascular outcomes. The main study outcome was the composite major adverse cardiovascular events (MACE) and its components. This outcome included fatal and non-fatal MI, fatal and non-fatal stroke along with CV death. An expanded MACE outcome (MACE-expanded), which additionally includes foot amputation, was also considered. The microvascular outcomes reported include nephropathy, neuropathy and retinopathy. Global outcomes of all-cause death, life years gained and the number needed to treat (NNT) to avoid each outcome was also reported.

Results

Demographics, Biomarkers, and Medication Use

Baseline characteristics of our study cohort are shown in Table 2. The average patient age was 54 years, with an average duration of diabetes of 7 years. Metformin was taken by 43% of the population, while 50% were taking an SU, and 7% a TZD. Eight percent had a history of MI, and 6% had a history of stroke.

Table 2. Baseline biomarker means, medication usage, and disease history of patients with T2DM uncontrolled on monotherapy.

Number of subjects	29 878
Demographics	
Age (years)	53.9
Gender (%)	
Male	51%
Female	49%
Race (%)	
White	66%
Black	14%
Other	20%
Biomarkers	
Current smoker (%)	20%
Glucose	
HbA1c (%)	7.9
FPG (mmol/L)	9.99
Lipids (mmol/mol)	
Total cholesterol	5.18
LDL-C	2.90
HDL-C	1.14
Triglycerides	2.54
Blood pressure (mm Hg)	
Systolic blood pressure	129.8
Diastolic blood pressure	74.7
Body mass	
BMI (kg/m^2)	34.1
Weight (kg)	96.5
Disease history	
Diabetes duration (years)	7.0
History of MI (%)	7.8%
History of stroke (%)	5.9%
Medications (% taking treatment)	
Diabetes medications	
Metformin	43%
Sulfonylurea	50%
TZD	7%
Insulin	0%
GLP-1 receptor agonist	0%
DPP-4 inhibitor	0%
Antihypertensive agents	
Any antihypertensive	41%
ACEI/ARB	34%
Beta-blocker	18%
CCB	13%
Diuretic	17%
Statin	37%
Aspirin	36%

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CCB, calcium channel blocker; DPP-4, dipepetidtyl peptidase-4; GLP-1, glucagon-like peptide-1; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; TZD, thiazolidinedione; T2DM, type 2 diabetes mellitus.

The time series for HbA1c, weight and SBP in each treatment strategy are shown in Figure 1a–c, and the time series of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG) and low-density lipoprotein cholesterol (LDL-C) are shown in Figure 2a–d. Treatment effects are immediate but only appear in the figures at the first year because biomarkers are recorded annually. The biomarker

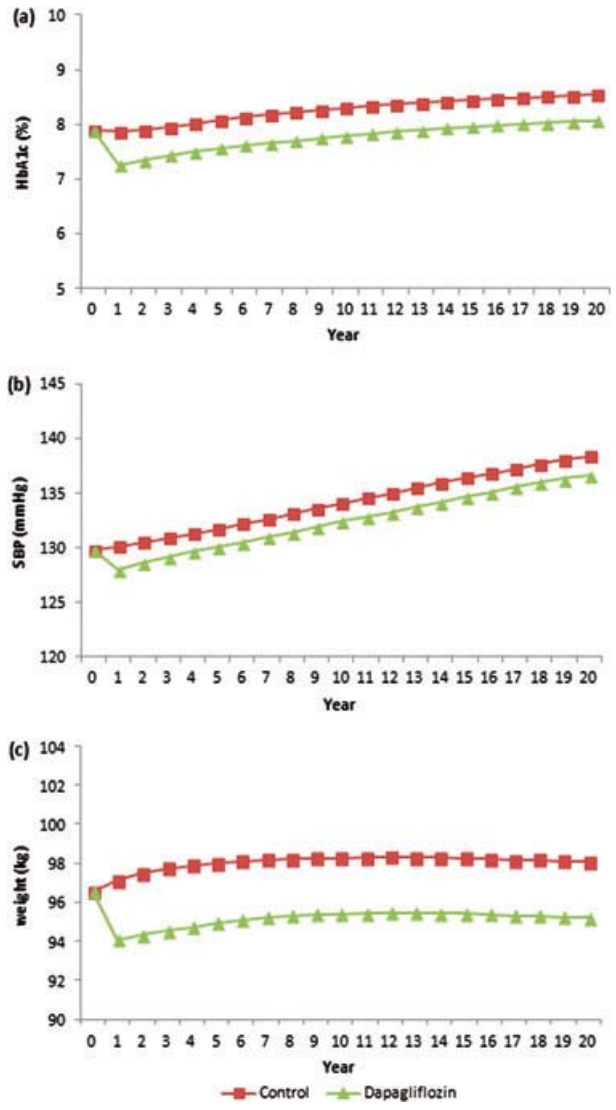

Figure 1. Time series for (a) HbA1c, (b) SBP, and (c) weight biomarkers of SOC and dapagliflozin treatment arms both dapagliflozin-1 and dapagliflozin-2 have the same effects on HbA1c, SBP, and weight, so a single, general dapagliflozin arm is shown. (HbA1c, glycated hemoglobin; SBP, systolic blood pressure).

then continues to evolve over time as it would in the absence of the medication based on the NHANES data, but the treatment effect continues to be applied. Initial treatment effects persist, although biomarkers drift over time consistent with those observed in NHANES. Dapagliflozin-1 and dapagliflozin-2 show the expected reductions in biomarkers and their progression over time. SGLT2 inhibitors exhibit a slight increase in LDL-C. This effect is captured in dapagliflozin-2 as shown in Figure 2d.

It should be noted that the SOC arm is an active treatment arm, and thus does affect disease progression as patients take standard glucose lowering medications. Patients on average are observed to indicate increased usage of glucose lowering medications (SU/TZD/insulin/DPP4/GLP1) over time as determined by the standard treatment protocol. It is also seen that HbA1c tends to rise over time as the disease progression continues despite SOC controlling efforts. This is attributed to a difference in rates of progression and control. The fact that this is seen in the SOC arm speaks to the potential benefit of an additional add-on treatment.

Treatment prevalence for the different antidiabetic, antihypertensive and cholesterol lowering agents for the different trial arms are given in Table 3a–c. Metformin usage is fairly constant over time, because it is restricted to patients who start on metformin. Once patients are put on sulfonylurea or TZD, they are not put back on metformin; rather they would be advanced to sulfonylurea, TZD, DPP-4, GLP1 and/or insulin at that point. The small decrease over time is because of metformin users who develop stage 4 or more severe CKD or systolic CHF and therefore become contraindicated to metformin. Sulfonylurea, TZD, DPP-4, GLP-1 and insulin usage increase at the start of the simulation as people who are uncontrolled advance to additional medications. Usage then levels off over time. Of note, fewer people in the dapagliflozin-1/2 arms advance to these treatments and those who do tend to do so later than in the SOC arm. SU usage exhibits an overall decrease over time in all of the arms as people develop contraindications to SU namely stage 3 CKD.

Health Outcomes

Twenty-year projections of CV and microvascular outcomes along with the relative differences between dapagliflozin and SOC treatment strategies are shown in Figure 3. All outcomes evaluated are significantly reduced.

The Model projects that over one-third of the uncontrolled T2DM cohort will have a MACE within 20 years when treated with SOC. Treatment with dapagliflozin-1 and dapagliflozin-2 in addition to SOC gives a relative reduction in MACE outcomes of 7.7% (95% CI: 6.6, 8.7%) and 10.4% (95 CI: 9.3, 11.6%), respectively, compared to SOC alone (Figure 3; Table 4). The largest relative reductions are projected for MI (9.5 and 13.8%, respectively). Significant reductions are also projected for all-cause death 4.3% (95% CI: 3.5, 5.0%) and 5.0% (95 CI: 4.1, 5.7%), respectively (Table 5).

When dapagliflozin is added to SOC, our analysis projects significant reductions in microvascular outcomes compared with current SOC alone. The two scenarios with dapagliflozin treatment as options show similar reductions in events, with the largest reductions in end-stage renal disease (ESRD) incidence (19.0 and 18.7% relative reductions for dapagliflozin-1 and dapagliflozin-2, respectively).

The NNT with dapagliflozin-1 or dapagliflozin-2 (given in addition to SOC) to avoid an outcome compared with SOC is presented in Table 5 and Figure 4. The analysis projects that diabetic retinopathy has the lowest NNT for both dapagliflozin-1 and dapagliflozin-2 treatments ($N = 15$ for both variants of dapagliflozin). Foot ulcer, MACE, MACE expanded and MI outcomes also have low NNT results (< 50).

Discussion

We used the Archimedes Model to project 20-year CV and microvascular outcomes among patients with T2DM

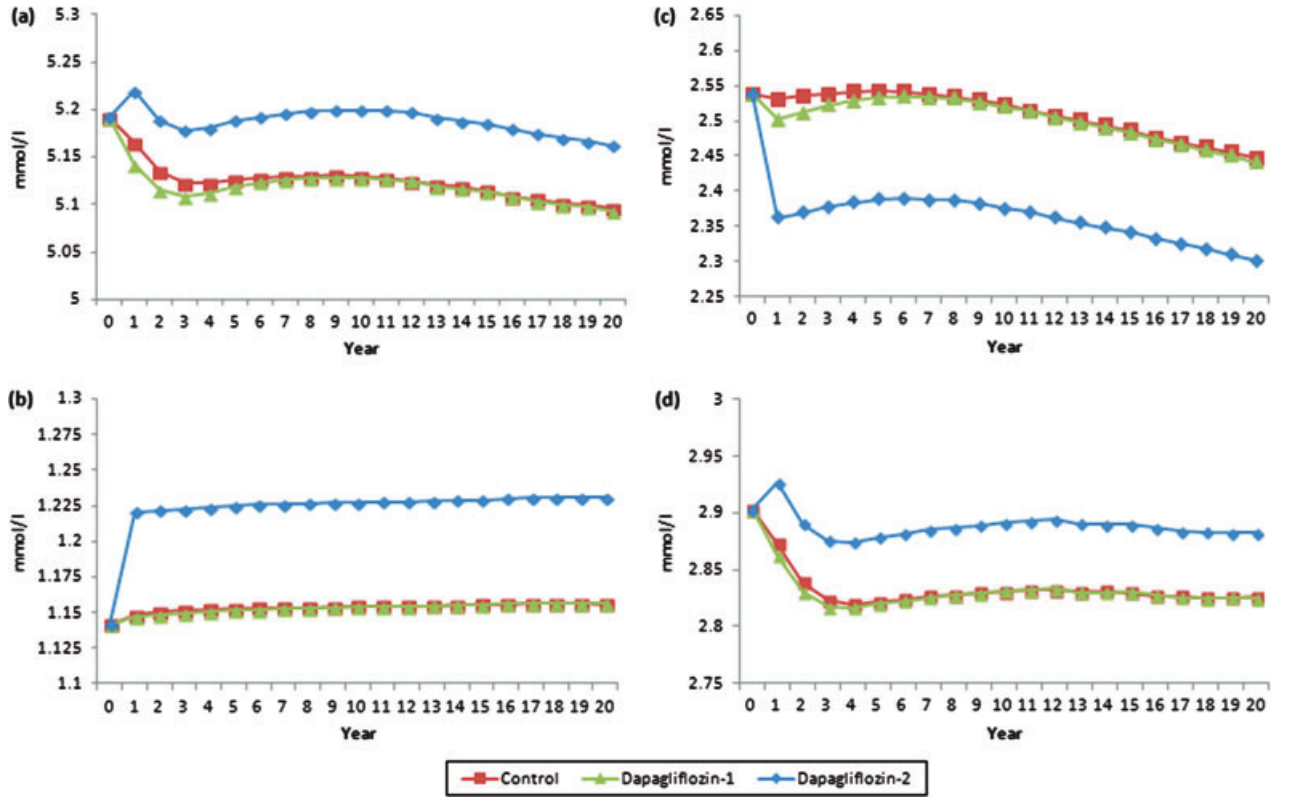

Figure 2. Time series for (a) TC, (b) HDL-C, (c) TG, (d) LDL-C of SOC and dapagliflozin treatment arms. (TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol).

Table 3. Treatment prevalence for different antidiabetic agents, as well as prevalence for any antihypertensives and any statins in the control (a), dapagliflozin-1 (b), and dapagliflozin-2 (c) arms.

(a)								
Year	Metformin (%)	Sulfonylurea (%)	TZD (%)	DPP-4 (%)	GLP-1 (%)	Insulin (%)	Any statin (%)	Any antihypertensive (%)
0	43.3	50.2	6.5	0.0	0.0	0.0	36.6	41.4
5	42.6	54.7	11.5	6.1	1.8	24.5	47.3	55.6
10	41.6	52.9	11.3	6.2	1.9	26.5	49.0	67.7
15	39.9	50.3	11.3	6.4	1.9	27.4	50.5	77.1
20	38.2	47.8	11.0	6.6	2.0	28.6	52.1	83.6
(b)								
Year	Metformin (%)	Sulfonylurea (%)	TZD (%)	DPP-4 (%)	GLP-1 (%)	Insulin (%)	Any statin (%)	Any antihypertensive (%)
0	43.3	50.2	6.5	0.0	0.0	0.0	36.6	41.4
5	42.7	52.6	9.3	3.7	1.1	14.0	47.1	51.9
10	41.8	52.7	10.7	5.6	1.6	21.8	48.9	64.1
15	40.2	50.4	10.9	6.0	1.7	24.0	50.3	74.4
20	38.9	48.1	10.8	6.4	1.7	25.4	52.0	81.6
(c)								
Time	Metformin (%)	Sulfonylurea (%)	TZD (%)	DPP-4 (%)	GLP-1 (%)	Insulin (%)	Any statin (%)	Any antihypertensive (%)
0	43.3	50.2	6.5	0.0	0.0	0.0	36.6	41.4
5	42.7	52.6	9.3	3.7	1.1	14.0	49.1	51.8
10	41.8	52.8	10.7	5.6	1.6	21.8	50.6	64.0
15	40.3	50.4	10.9	6.0	1.7	23.9	52.0	74.3
20	39.0	48.1	10.8	6.4	1.8	25.3	53.6	81.4

TZD, thiazolidinedione; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1.

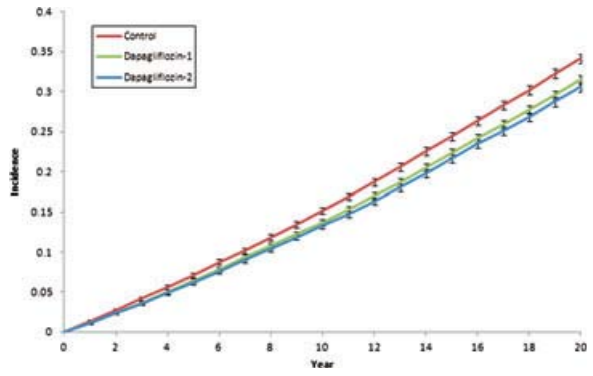

Figure 3. Kaplan–Meier plot of MACE for the control, dapagliflozin-1 and dapagliflozin-2 arms reported annually up to 20 years for the uncontrolled type 2 diabetes mellitus (T2DM) cohort. [MACE, major adverse cardiovascular events (fatal and non-fatal myocardial infarction (MI); fatal and non-fatal stroke along with cardiovascular (CV) death)].

Table 4. Kaplan–Meier event rate data for MACE reported at 5 year intervals of the simulation.

	Trial arm		
Year	SOC	Dapagliflozin 1	Dapagliflozin 2
5	0.071 (0.068, 0.074)	0.064 (0.061, 0.067)	0.062 (0.060, 0.065)
10	0.152 (0.148, 0.156)	0.137 (0.133, 0.141)	0.133 (0.129, 0.137)
15	0.244 (0.239, 0.249)	0.223 (0.218, 0.228)	0.216 (0.211, 0.221)
20	0.341 (0.335, 0.347)	0.315 (0.309, 0.321)	0.306 (0.300, 0.311)

SOC, standard of care; MACE, major adverse cardiovascular events.

uncontrolled on monotherapy at baseline. The simulated trial included three treatment strategies: one representing SOC today and two that added dapagliflozin to the SOC T2DM treatment options. We modeled two variants of dapagliflozin.

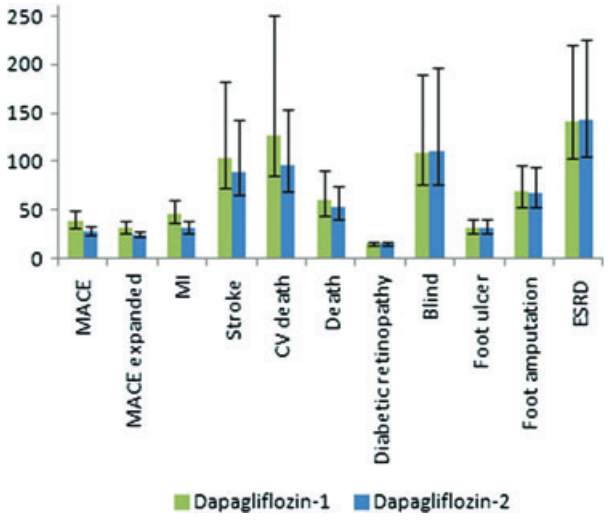

Figure 4. Number needed to treat with dapagliflozin-1 and dapagliflozin-2 treatments to avoid an outcome relative to standard of care (SOC) at 20 years among uncontrolled type 2 diabetes mellitus (T2DM) cohort. [MACE, major adverse cardiovascular events (fatal and non-fatal MI, fatal and non-fatal stroke along with CV death), expanded MACE, MACE and foot amputation; MI, myocardial infarction; CV, cardiovascular; ESRD, end-stage renal disease].

The first, dapagliflozin-1, included the glucose-, BP-, weight- and SUA-lowering effects associated with dapagliflozin. The second, dapagliflozin-2, included these effects plus effects on lipids. Our analyses projected that dapagliflozin significantly reduces all studied CV and microvascular outcomes when given in addition to SOC, compared with current SOC.

When dapagliflozin is available in SOC treatment, the largest reductions in CV outcomes were seen in MI with a 9.5% relative reduction (95% CI: 8.1–11.0%) and 13.8%

Table 5. Cardiovascular and microvascular Kaplan–Meier event rates at year 20 of the simulation, relative differences in dapagliflozin-1 and dapagliflozin-2 treatments compared with SOC and NNT.

		Relative difference (95% CI) in KM event rates of dapagliflozin to SOC		Number needed to treat (95% CI) with dapagliflozin compared to SOC	
Event	SOC KM event rates (95% CI)	Dapagliflozin-1	Dapagliflozin-2	Dapagliflozin-1	Dapagliflozin-2
MACE	0.341 (0.335, 0.347)	−7.7% (−8.7, −6.6%)	−10.4% (−11.6, −9.3%)	38 (31, 49)	28 (24, 34)
Expanded MACE	0.405 (0.399, 0.411)	−7.9% (−8.8, −7.0%)	−10.0% (−11.0, −9.0%)	31 (26, 39)	25 (22, 29)
MI	0.226 (0.221, 0.232)	−9.5% (−11.0, −8.1%)	−13.8% (−15.5, −12.1%)	46 (37, 61)	32 (27, 38)
Stroke	0.122 (0.117, 0.126)	−7.9% (−9.9, −5.9%)	−9.1% (−11.2, −7.0%)	104 (73, 182)	90 (66, 143)
CV death	0.109 (0.105, 0.113)	−7.3% (−9.6, −4.9%)	−9.6% (−12.1, −7.0%)	127 (85, 251)	96 (70, 154)
All-cause death	0.387 (0.381, 0.392)	−4.3% (−5.0, −3.5%)	−5.0% (−5.7, −4.1%)	61 (45, 91)	53 (41, 75)
Diabetic retinopathy	0.686 (0.679, 0.692)	−9.7% (−10.4, −9.0%)	−9.8% (−10.5, −9.1%)	15 (14, 17)	15 (14, 17)
Blindness	0.107 (0.103, 0.111)	−8.6% (−11.3, −5.9%)	−8.4% (−11.1, −5.7%)	109 (76, 189)	111 (77, 197)
Foot ulcer	0.372 (0.366, 0.378)	−8.3% (−9.0, −7.6%)	−8.3% (−9.0, −7.6%)	32 (27, 40)	32 (27, 40)
Foot amputation	0.113 (0.108, 0.117)	−12.8% (−14.6, −11.0%)	−13.0% (−14.8, −11.1%)	69 (54, 97)	68 (53, 95)
ESRD	0.037 (0.035, 0.04)	−19.0% (−23.6, −14.7%)	−18.7% (−23.0, −14.5%)	141 (104, 220)	143 (105, 225)

MACE, major adverse cardiovascular events (fatal and non-fatal MI, fatal and non-fatal stroke along with CV death); expanded MACE, MACE and foot amputation; MI, myocardial infarction; CV, cardiovascular; ESRD, end-stage renal disease; CI: confident intervals; KM, Kaplan–Meier; SOC, standard of care.

(95% CI: 12.1–15.5%) in dapagliflozin-1 and dapagliflozin-2, respectively. In addition, NNT to avoid a MACE, expanded MACE, or MI outcome was relatively low (NNT between 25 and 46). Studies designed to address the value of intensive glycaemic control in preventing macrovascular outcomes among patients with T2DM have yielded a mixed picture of the relative benefit [31,33], although our findings in these analyses are within the above range.

Benefits of dapagliflozin treatment projected for microvascular outcomes varied based on the relative importance of glucose, BP and weight control to these conditions. In sensitivity analyses we found all retinopathy, neuropathy and nephropathy outcomes were significantly reduced by dapagliflozin's effects on HbA1c alone, with relative reductions ranging from 3.6 to 8.9%, compared with SOC. In contrast, dapagliflozin's effects on weight alone and SBP alone reduced ESRD incidence by 4.8 and 6.5%, respectively, while other microvascular outcomes had smaller relative reductions (ranging from no effect to less than 2%).

Both dapagliflozin-1 and dapagliflozin-2 significantly reduced all-cause mortality and increased life-years. Our analyses projected that dapagliflozin-1 and dapagliflozin-2 should lead to relative reductions in death of 4.3 and 5.0%, respectively, over 20 years, when taken in addition to SOC. This is approximately 160 and 185 life-years gained per 1000 people treated over 20 years, compared with SOC alone.

Findings highlight the potential additional benefits of adding dapagliflozin to SOC while following ADA/EASD guidelines. These results are consistent with previously published findings that dapagliflozin improves glycaemic control and allows more individuals to achieve goals [7,8,10] and also extend this work by projecting reductions in CV and microvascular outcomes. It could also be of considerable interest for possible future work in this area to compare a DPP-4 inhibitor based strategy and an SGLT2 inhibitor based strategy with SOC. For any potential future benefit/economic analysis of dapagliflozin, however, it could be useful to also include the increased risk of genital/urinary tract infections in the analysis.

It should be noted that dapagliflozin is approved for use in the European Union but is not yet approved by the FDA for use in the United States. These findings are applicable to the US as well as European countries with similar baseline risk and quality of healthcare.

The two variants of dapagliflozin examined in these analyses differ only in their effects on the lipid panel. Although effects of dapagliflozin on the lipid panel have been observed in clinical trials [7–10] these results have not been demonstrated conclusively and shows some inconsistencies. Findings show HDL-C and TG are improved while TC worsens slightly. We include the dapagliflozin-2 variant as an experimental scenario. In our analysis the benefits to HDL-C and TG countered effects of raised TC.

With new interventions to reduce SUA in the development and approval pipeline, there is a growing body of evidence to suggest the importance of SUA on MI, stroke, CV death, and all-cause death [34]. The SGLT-2 class of drugs shows significant benefits in glycaemic control along with reductions in SUA [35]. We found that the inclusion of the SUA pathway in our model of dapagliflozin had a significant impact on CV outcomes. In comparison with SOC, dapagliflozin's effect on SUA nearly doubled the relative reduction projected for MACE outcomes when dapagliflozin-1 was taken in addition to SOC, and raised by a third when dapagliflozin-2 was taken in addition to SOC. With limited data, it is difficult to determine how realistic our maximal effects model is, although it appears to align well with reductions in risk associated with losartan use in the LIFE study. This study found the relative risk of MI per mg/dl of SUA to be 1.125 in women and 1.024 in men when controlling for traditional risk factors [23], whereas our meta-analysis found 1.152 and 1.042, respectively, where 1 mg/dl of SUA = 59.48 μmol/l of SUA.

Conclusion

This study shows that dapagliflozin in addition to currently available treatment options decrease the macrovascular and microvascular complications associated with T2DM. These projections have potentially significant clinical relevance as they show low NNT for early-stage diabetes complications (NNT between 15 and 32) as well as the expanded MACE outcome (NNT = 31 and 25 for dapagliflozin-1 and dapagliflozin-2, respectively).

Conflict of Interest

J. R. and E. H. are employees of AstraZeneca. U. I. and I. P. are employees of Bristol-Myers Squibb.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Description of the serum uric acid (SUA) model.

References

1. World Health Organization Media Center Diabetes Fact Sheet. Available from URL: http://www.who.int/mediacentre/factsheets/fs312/en/index.html. Accessed 14 November 2012.
2. Gaede P, Vedel P, Parving HH, Pedersen O. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomized study. Lancet 1999; **353**: 617–622.
3. Tzoulaki I, Molokhia M, Curcin V et al. Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database. BMJ 2009; **339**: b4731.
4. Inzucchi SE, Bergenstal RM, Buse JB et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. A Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012.
5. Ford ES. Trends in the risk for coronary heart disease among adults with diagnosed diabetes in the US. Diabetes Care 2011; **34**: 1337–1343.
6. Ford ES. Trends in the control of risk factors for cardiovascular disease among adults with diagnosed diabetes: findings from the National Health and Nutrition Examination Survey 1999–2008. J Diabetes 2011; **3**: 337–347.

7. Strojek K, Yoon KH, Hruba V, Elze M, Langkilde AM, Parikh S. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with glimepiride: a randomized, 24-week, double-blind, placebo-controlled trial. Diabetes Obes Metab 2011; **13**: 928–938.
8. Rosenstock J, Vico M, Wei L, Salsali A, List JF. Effects of dapagliflozin, a sodium-glucose cotransporter-2 inhibitor, on hemoglobin A1c, body weight, and hypoglycemic risk in patients with type 2 diabetes inadequately controlled on pioglitazone monotherapy. Diabetes Care 2012; **35**: 1473–1478.
9. Nauck MA, Prato SD, Meier JJ et al. Dapagliflozin versus glipizide as add-on therapy in patients with type 2 diabetes who have inadequate glycemic control with metformin a randomized, 52-week, double-blind, active-controlled noninferiority trial. Diabetes Care 2011; **34**: 2015–2022.
10. Bailey CJ, Gross JL, Pieters A, Bastien A, List JF. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomized, double-blind, placebo-controlled trial. Lancet 2010; **375**: 2223–2233.
11. Cefalu WT, Leiter LA, Debruin TW, Gause-Nilsson I, Sugg JE, Parikh SJ. Dapagliflozin treatment for type 2 diabetes mellitus patients with comorbid cardiovascular disease and hypertension. In: 72nd ADA Scientific Session Poster Presentation 2012, 1056-P
12. Leiter LA, Cefalu WT, Debruin TW, Gause-Nilsson I, Sugg JE, Parikh SJ. Efficacy and safety of dapagliflozin for type 2 diabetes mellitus patients with a history of cardiovascular disease. In: 72nd ADA Scientific Session Poster Presentation 2012, 1114-P
13. Gertler MM, Garn SM, Levine SA. Serum uric acid in relation to age and physique in health and in coronary heart disease. Ann Intern Med 1951; **34**: 1421.
14. Ulmer H, Kelleher CC, Fitz-Simon N, Diem G, Concin H. Secular trends in cardiovascular risk factors: an age-period-cohort analysis of 698,954 health examinations in 181,350 Austrian men and women. J Intern Med 2007; **261**: 566–576.
15. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: The Framingham heart study. Ann Intern Med 1999; **131**: 7–13.
16. Fang J, Alderman MH. Serum uric acid and cardiovascular mortality. The NHANES I epidemiologic follow-up study, 1971–1992. JAMA 2000; **283**: 2404–2410.
17. Johnson RJ, Tuttle KR. Much ado about nothing, or much to do about something? The continuing controversy over the role of uric acid in cardiovascular disease. Hypertension 2000; **35**: E10.
18. Baker JF, Krishnan E, Chen L, Schumacher HR. Serum uric acid and cardiovascular disease: recent developments, and where do they leave us? Am J Med 2005; **118**: 816–826.
19. Sakata K, Hashimoto T, Ueshima H, Okayama A, for the NIPPON DATA 80 Research Group. Absence of an association between serum uric acid and mortality from cardiovascular disease: NIPPON DATA 80, 1980–1994. Eur J Epidemiol 2001; **17**: 461–468.
20. Holme I, Aastveit AH, Hammar N, Jungner I, Walldius G. Uric acid and risk of myocardial infarction, stroke, and congestive heart failure in 417734 men and women in the Apolipoprotein MOrtality RISk study (AMORIS). J Intern Med 2009; **266**: 558–570.
21. Strasak AM, Kelleher CC, Brant LJ et al. Serum uric acid is an independent predictor for all major forms of cardiovascular death in 28613 elderly women: a prospective 21-year follow-up study. Int J Cardiol 2008; **125**: 232–239.
22. Moriarity JT, Folsom AR, Iribarren C, Nieto FJ, Rosamond WD. Serum uric acid and risk of coronary heart disease: Atherosclerosis Risk in Communities (ARIC) study. Ann Epidemiol 2000; **10**: 136–143.
23. Hoieggen A, Alderman MH, Kjeldsen SE, Julius S et al, for the LIFE Study Group. The impact of serum uric acid on cardiovascular outcomes in the LIFE study. Kidney Int 2004; **65**: 1041–1049.
24. Athyros VG, Elisaf M, Papageorgiou AA et al, for the GREACE Study Collaborative Group. Effect of statins versus untreated dyslipidemia on serum uric acid levels in patients with coronary heart disease: a subgroup analysis of the GREek Atorvastatin and Coronary-heart-disease Evaluation (GREACE) study. Am J Kidney Dis 2004; **43**: 589–599.
25. Luk AJ, Levin GP, Moore EE, Zhou XH, Kestenbaum BR, Choi HK. Allopurinol and mortality in hyperuricemic patients. Rheumatology 2009; **48**: 804–806.
26. ZHU Wen-hua, FANG Li-zheng, CH Li-ying, CHEN Zhou-wen, DAI-Hong-Lei, CHEN Jian-hua Follow-up study of programmed intervention of hyperuricemia in the prevention and treatment of cardiovascular morbid change Natl Med J China 2010; **90**: 662–666.
27. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. N Engl J Med 2008; **359**: 1811–1821.
28. Eddy DM, Schlessinger L. Archimedes: a trial-validated model of diabetes. Diabetes Care 2003; **26**: 3093–3101.
29. Eddy DM, Schlessinger L. Validation of the Archimedes diabetes model. Diabetes Care 2003; **26**: 3102–31110.
30. Eddy DM, Schlessinger L, Kahn R. Clinical outcomes and cost-effectiveness of strategies for managing people at high risk for diabetes. Ann Intern Med 2005; **143**: 251–264.
31. Alperin P, Soto-Campos G, Peskin B et al. Understanding the effect of glycemic control on macrovascular outcomes in patients with diabetes using the Archimedes model. American Diabetes Association Scientific Sessions: Orlando, FL, 2010.
32. The Mount Hood 4 Modeling Group. Computer modeling of diabetes and its complications. Diabetes Care 2007; **30**: 1638–1646.
33. Ray KK, Seshasai SR, Wijesuriya S et al. Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus; a meta-analysis of randomized controlled trials. Lancet 2009; **373**: 1765–1772.
34. Schemacher HR, Becker MA, Wormann RL et al. Effects of febuxostat versus allopurinol and placebo in reducing serum urate in subjects with hyperuricemia and gout: a 28-week, phase III, randomized, double-blind, parallel-group trial. Arthritis Rheum 2008; **59**: 1540–1548.
35. Rosenstock J, Aggarwal N, Polidori D et al. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. Diabetes Care 2012; **35**: 1232–1238.