CADTH

CADTH COMMON DRUG REVIEW

Pharmacoeconomic Report

DAPAGLIFLOZIN (FORXIGA)

(AstraZeneca Canada Inc.)

Indication: Heart failure with reduced ejection fraction

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Table of Contents

Tables

Figures

Abbreviations

ACEI	angiotensin-converting enzyme inhibitor
ARB	angiotensin receptor blocker
BIA	budget impact analysis
CV	cardiovascular
DAPA	dapagliflozin
HFrEF	heart failure with reduced ejection fraction
HHF	hospitalization for heart failure
ICER	incremental cost-effectiveness ratio
MAIC	matching-adjusted indirect comparison
MRA	mineralocorticoid receptor antagonist
NHYA	New York Heart Association
QALY	quality-adjusted life-year
SAC	sacubitril
SGLT2	sodium-glucose cotransporter-2
ST	standard therapy
T2DM	type 2 diabetes mellitus
VAL	valsartan

Executive Summary

The executive summary is composed of 2 tables (Table 1 and Table 2) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Dapagliflozin (Forxiga) 5 mg and 10 mg oral tablets
Submitted price	Dapagliflozin 5 mg and 10 mg oral tablets: $2.73
Indication	In adults, as an adjunct to standard of care therapy, for the treatment of heart failure with reduced ejection fraction to reduce the risk of cardiovascular death, hospitalization for heart failure and urgent heart failure visit
Health Canada approval status	Approved
Health Canada review pathway	Priority review
NOC date	June 29, 2020
Reimbursement request	As per indication
Sponsor	AstraZeneca Canada Inc.
Submission history	Previously reviewed: Yes Type 2 diabetes mellitus in combination with metformin, sulfonylurea, or insulin (± metformin) Indication: For use in patients with type 2 diabetes mellitus to improve glycemic control in combination with: • metformin, when the existing therapy, along with diet and exercise, does not provide adequate glycemic control • a sulfonylurea, when the existing therapy, along with diet and exercise, does not provide adequate glycemic control • insulin (alone or with metformin), when the existing therapy, along with diet and exercise, does not provide adequate glycemic control. Recommendation date: November 20, 2015 Recommendation: List with clinical criteria and/or conditions Type 2 diabetes mellitus in combination with metformin and a sulfonylurea Indication: For use in patients with type 2 diabetes mellitus to improve glycemic control in combination with metformin and a sulfonylurea, when the existing therapy, along with diet and exercise, does not provide adequate glycemic control Recommendation date: April 27, 2016 Recommendation: Do not list

NOC = Notice of Compliance.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Markov model
Target population	Heart failure with reduced ejection fraction
Treatment	Dapagliflozin plus standard therapy (DAPA + ST)
Comparators	• Standard therapy (ST), which consists of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, mineralocorticoids/aldosterone antagonists, and sacubitril-valsartan (SAC-VAL) • SAC-VAL + ST (scenario analysis)
Perspective	Canadian publicly funded health care payer
Outcome(s)	QALYs
Time horizon	Lifetime (34.67 years)
Key data source	DAPA-HF clinical trial
Submitted results for base case (and key scenario analyses as required)	ICER for DAPA + ST versus ST = $11,092 per QALY; DAPA + ST was associated with higher costs (incremental: $6,562) and more QALYs (incremental: 0.592)
Key limitations	• The economic submission (model and report) lacked transparency and flexibility. CADTH identified errors in the submitted model, which required correction by the sponsor, and is concerned that there may still be outstanding issues that have not been identified, given the complexity of the model approach. Despite a request from CADTH, this limitation with model presentation has not been addressed by the sponsor. • Based on CADTH guidance from clinical experts for target populations, analysis stratified by NYHA class should be the primary analysis (NYHA II and III–IV). Analyses by NYHA class were not conducted by the sponsor. • The sponsor stated in the submitted report that no difference in mortality between therapies for patients in NYHA classes III and IV were assumed, but the model included a mortality benefit for DAPA + ST contrary to the DAPA-HF trial. • The model predicted that a high proportion of patients' NYHA status would improve, which is contrary to what is known about heart failure. • Heart failure hospitalizations and the costs of cardiovascular deaths (which would cover hospitalization costs) are both included in the model, likely resulting in double counting of hospital costs. • The CADTH Clinical Review states that no conclusions can be drawn from the matching-adjusted indirect comparison of DAPA + ST versus SAC-VAL + ST. Thus, no comparison in terms of cost-effectiveness can be made.
CADTH reanalysis results	• For patients in NYHA class II, the ICER for DAPA + ST versus ST was $8,760. • For patients in NYHA classes III or IV, DAPA + ST was dominated by ST. DAPA + ST is associated with higher costs and fewer QALYs. • No comparison could be made with SAC-VAL + ST.

ICER = incremental cost-effectiveness ratio; NYHA = New York Heart Association; QALY = quality-adjusted life-year.

Conclusions

For patients in New York Heart Association (NYHA) class II, the incremental cost-effectiveness ratio (ICER) for dapagliflozin plus standard therapy (DAPA + ST) versus standard therapy (ST) is $8,760 per quality-adjusted life-year (QALY). For patients in class III or IV, DAPA + ST is dominated by ST: DAPA + ST is more costly and associated with fewer QALYs. This result was associated with uncertainty given the evidence regarding the clinical efficacy of DAPA + ST in NYHA classes III and IV, as shown in the DAPA-HF trial. Given concerns with the lack of robust clinical information to inform the comparison of DAPA + ST and sacubitril-valsartan plus standard therapy (SAC-VAL + ST), the cost-effectiveness of DAPA + ST versus SAC-VAL + ST in this indication cannot be assessed. CADTH expressed concern over the lack of flexibility and transparency with the submitted model. While the submission is not representative of best practices, the limitations are unlikely to impact the conclusion that, based on the DAPA-HF trial evidence for DAPA + ST efficacy by NYHA class, DAPA + ST is cost-effective for patients in NYHA class II but not for patients in classes III or IV.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups that participated in the CADTH review process (specifically, information that pertains to the economic submission).

Three patient groups — the HeartLife Foundation, the Heart Failure Support Group of Manitoba, and the Cardiac Health Foundation of Canada — provided input to the CADTH review of dapagliflozin (DAPA).

The patient groups described the chronic nature of heart failure and acknowledged that while there is no cure for the condition, the patients hoped for treatments that would stabilize their condition and symptoms. Challenges that patients associated with living with heart failure included difficulty in performing activities of daily living, fatigue, shortness of breath with physical activities, edema, and disturbed sleep. Some patients also described the impact of heart failure on their mental health, noting concerns regarding depression and anxiety. Patients expressed a desire to be able to conduct activities of daily living with less shortness of breath, to experience improved symptoms, and to reduce the risk of hospitalization and cardiovascular (CV)-related mortality. Patients also expressed a desire for an improvement in their quality of life, which included spending more time with loved ones and the ability to enjoy outdoor activities, go to work, and travel. Finally, patients generally spoke of desire that a new treatment would reduce adverse events.

Many participating patients reported being on triple therapy (angiotensin-converting enzyme inhibitor [ACEI] or angiotensin receptor blocker [ARB], beta-blockers, and mineralocorticoid receptor antagonists [MRAs]). Some patients expressed a concern regarding taking too many medications, which, given that DAPA is an add-on to standard of care, might make it undesirable for some patients. One patient had taken DAPA previously, and 2 others were on a different sodium-glucose cotransporter-2 (SGLT2)inhibitor. No details were provided on how these treatments impacted the patients' condition.

- The sponsor's model accounted for some elements of the patient input identified, although not all aspects of the patient input were captured:
- The sponsor included as part of standard of care an ACEI or ARB, a beta-blocker, and an MRA, with or without SAC-VAL, which some participating patients also noted using.
- The sponsor modelled transitions between NYHA classes, a measurement of disease severity based on patient symptoms, including limitations in physical activity, fatigue, and shortness of breath, meaning these results should be relevant to patients.[1] Disturbed sleep and edema were not symptoms explicitly considered in the model.
- The economic model included hospitalization and CV mortality outcomes. Adverse events were also considered in the model.
- Quality of life was included through health state utility values applied to NYHA classes and utility decrements associated with hospitalization and some adverse events.

Economic Review

The current review is for DAPA (Forxiga) for patients with heart failure with reduced ejection fraction (HFrEF).

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The patient population studied within this submission corresponds to the eligibility criteria of the DAPA-HF clinical study: adults with heart failure (NYHA class II, III, or IV) with reduced ejection fraction (≤ 40%).[2] The patient population aligns with both the Health Canada–indicated population and the reimbursement request.

The primary analysis compares DAPA + ST to ST alone.[3] Standard therapy consisted of ACEIs, ARBs, beta-blockers, and MRAs. Some patients within the ST arm received SAC-VAL as well. From the DAPA-HF trial, 56.1% of patients in the ST arm were receiving an ACEI, 26.7% an ARB, 71.5% an MRA, 96% a beta-blocker, and 10.9% SAC-VAL. Outcomes were assumed to be consistent regardless of what the primary drug therapy was. A secondary analysis was conducted comparing DAPA + ST to only SAC-VAL + ST. This secondary analysis was based on a sponsor-conducted matching-adjusted indirect comparison (MAIC), not the patients receiving SAC-VAL within the DAPA-HF trial.[4]

Dapagliflozin was dosed at 1 tablet of 10 mg daily. This was priced at $2.73 per tablet. This leads to an annual treatment cost for DAPA of $1,182.13, inclusive of an 8% markup and twelve $8.83 prescription charges. The annual treatment cost of ST included in the model was $694.27. In the report, this was stated to be the sum of the treatment costs of ACEI, ARB, and SAC-VAL, weighted by their use in the DAPA-HF trial.[3] However, lack of transparency in reporting and within the model submitted led to CADTH being unable to verify the derivation of this cost. The model did not include any allowance for wastage, though it is likely to occur.

The analysis modelled the following outcomes: transition between NYHA class, mortality (both CV and non-CV), hospitalization for heart failure (HHF), urgent heart failure visits, and adverse events (volume depletion, renal events, hypoglycemic events, fractures, diabetic ketoacidosis, and amputation).

The analysis was conducted from the perspective of a provincial ministry of health with a lifetime time horizon (capped at 34.67 years). A discount rate of 1.5% per annum was applied.

Model Structure

The sponsor's submission took the form of a Markov model with a lifetime horizon (34.67 years) with a monthly cycle length.[3] The model comprised 17 health states relating to the patient's NYHA class (I, II, III, and IV), whether they had type 2 diabetes mellitus (T2DM), whether they were still on DAPA + ST, and the absorbing state (death). Thus, the health states included were as follows:

- NYHA class I, no T2DM, not on DAPA + ST
- NYHA class II, no T2DM, not on DAPA + ST

- NYHA class III, no T2DM, not on DAPA + ST
- NYHA class IV, no T2DM, not on DAPA + ST
- NYHA class I, no T2DM, on DAPA + ST
- NYHA class II, no T2DM, on DAPA + ST
- NYHA class III, no T2DM, on DAPA + ST
- NYHA class IV, no T2DM, on DAPA + ST
- Death
- NYHA class I, with T2DM, not on DAPA + ST
- NYHA class II, with T2DM, not on DAPA + ST
- NYHA class III, with T2DM, not on DAPA + ST
- NYHA class IV, with T2DM, not on DAPA + ST
- NYHA class I, with T2DM, on DAPA + ST
- NYHA class II, with T2DM, on DAPA + ST
- NYHA class III, with T2DM, on DAPA + ST
- NYHA class IV, with T2DM, on DAPA + ST

Patients transitioned monthly between NYHA class, with a risk of death that was estimated to be higher for patients in NYHA classes III or IV. In addition, the risk of death was lower for patients receiving DAPA + ST who were in classes I or II. The probability of patients dying each month and the probability of an HHF increased over time regardless of which state the patient was in. Patients on DAPA + ST could also transition into a "not on DAPA + ST" health state based on an assumed discontinuation rate. Patients who did not have T2DM were assumed not to transition to T2DM.

In addition to the transitions between health states, the model provides estimates of the proportion of the cohort who experience the following 3 events each cycle: HHF, urgent heart failure visit, or CV death. The likelihood of each event occurring is influenced by NYHA class, whether the patient is on DAPA + ST, and whether the patient has T2DM. The following adverse events associated with treatment were included: volume depletion, renal events, hypoglycemic events, fractures, diabetic ketoacidosis, and amputation.[3]

The model submitted did not transparently detail the actual formulas used to estimate the transition of the patients across states and the events such as HHFs and adverse events. Furthermore, for patients receiving DAPA + ST, the model provides the number of patients in each NYHA state with and without T2DM but does not distinguish between those remaining on DAPA + ST and those who have discontinued and moved to ST alone. Thus, differences in the distribution across NYHA states between those continuing therapy and those not continuing therapy are not provided and could not be validated (Appendix 3, Figure 1 and Figure 2).

Model Inputs

The patient cohort within the model represented the clinical trial population from the DAPA-HF study.[2,3] Patients were characterized by age at study entry; sex; body mass index; NYHA class; N-terminal pro B-type natriuretic peptide level; creatinine level; left ventricular ejection fraction; and the proportion of the patients who have T2DM, ischemic heart failure, and/or

prior HHF and who have had heart failure for more than 2 years. The model provided the option of stratifying patients by NYHA class (II or III–IV), T2DM (yes or no), prior HHF (yes or no), and age (≤ 65 or > 65). For these analyses, a strata-specific baseline population was employed.[3]

Data on the transition of patients between NYHA classes were derived from the DAPA-HF trial.[2] Given no treatment effect, in terms of movement through NYHA class, was identified in the trial, transitions were assumed the same for both DAPA + ST and ST. Full details on how these transition probabilities were derived were not provided.

Based on the patient's baseline characteristics, NYHA class, and treatment received, the model estimates the proportion of patients who will die each cycle (both CV and non-CV mortality) as well as the occurrence of HHFs, urgent heart failure visits, and adverse events.

For mortality, the model does not use hazard ratios for mortality from the clinical trial but rather uses 2 adjusted parametric survival equations for CV mortality and all-cause mortality.[5] Both equations take the form of a Weibull model. Rather than assess different forms of survival functions based on appropriate consideration of statistical fit and clinical validity, as recommended, the sponsor chose a Weibull model based on the approach adopted in a previous study relating to heart failure.[6,7] Although the sponsor's model allows the adoption of different forms of survival function, the option to choose 1 form for all-cause mortality and another for CV mortality was not provided. In the sponsor's economic report it is stated that for the adjusted analysis, the hazard ratio for mortality associated with DAPA is only applied to patients in NYHA class I or II, which is consistent with DAPA-HF trial observations.[3,5]

Non-CV mortality is estimated by subtracting CV mortality from the estimated all-cause mortality. If the estimated non-CV mortality is less than the Canadian life table's estimate of non-CV mortality, then the Canadian life table's estimate of non-CV mortality is adopted.[8] UK life tables are provided as a reference of the Canadian life table's estimate of non-CV mortality.[8]

Hospitalization for HF and urgent HF visits are estimated using generalized estimating equations. The report explains that these were estimated using DAPA-HF trial data and estimated a reduction in events with DAPA + ST. Full details of these generalized estimating equations are not given — specifically, the choice of which function to use is not provided. For HHFs, the model assumes the rate of event increases with time. CADTH, in trying to replicate the model results, found a discordance in estimates of hospitalizations. This was explained by the sponsor as resulting from capping the increase in HHFs at 29 months, as including the time trend beyond this would lead to very high rates of hospitalization. This was not detailed in the original or the revised report.

A discontinuation rate for DAPA of 7% per annum was adopted and derived from the DAPA-HF clinical trial.[2] Adverse events for DAPA + ST and ST were derived from the DAPA-HF clinical trial.[2]

For the comparison of DAPA + ST versus SAC-VAL + ST, relative effectiveness was derived from the sponsor's MAIC.[4] Within the probabilistic analysis, the model assumes a relative effect (though with a confidence interval passing the line of no effect) in favour of DAPA + ST with respect to HHF, CV death, and all-cause mortality.

Utility values derived from the EuroQol 5-Dimensions questionnaire were estimated for each NYHA class from the DAPA-HF trial, along with decrements for T2DM, HHF, urgent heart

failure visits, volume depletion, renal events, and fractures.[2,9,10] Decrements for hypoglycemic events and amputations were obtained from the literature.[11-13] The submitted report states that decrements are applied to the NYHA utility values multiplicatively, but in the model they are applied as additive.

Costs for treatment regimens are obtained from the Ontario Drug Benefit Formulary, but full methods in terms of unit costs, volumes, and proportions for each drug are not provided.[14] The model includes an 8% markup and monthly prescription fees. CADTH would normally exclude these costs, but the lack of transparency in reporting and the non-flexible nature of the model does not allow for this. Health state event costs and adverse event costs were derived from the Canadian literature.[15-18]

Summary of Sponsor's Economic Evaluation Results

The sponsor submitted results based on probabilistic analyses with 1,000 iterations. A number of probabilistic scenario analyses were presented, as were a number of 1-way deterministic sensitivity analyses.

Base-Case Results

In the updated sponsor's base-case analysis from June 24, 2020, the ICER for DAPA + ST versus ST alone for the whole DAPA-HF population was $11,092 (Table 3). DAPA + ST was associated with higher costs ($44,594 versus $38,031) and more QALYs (5.151 versus 4.559). Higher costs were mainly due to higher treatment costs and higher management costs (due to longer life expectancy), which were partially offset by reduced costs of HHF. The greater number of QALYs was due to greater time spent in NYHA class I and II as result of increased life expectancy rather than differences in progression (Appendix 3, Table 13).

Results are highly reliant on the estimated benefit in the extrapolated period (i.e., post 2-year trial period), with only 3.7% of the QALY benefit from DAPA + ST (0.022 out of 0.595, based on deterministic analysis) accumulated within 2 years. The probability that DAPA + ST is cost-effective compared to ST alone at a threshold of $50,000 per incremental QALY was reported as 90%.

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug	Total costs, $	Incremental costs, $	Total QALYs	Incremental QALYs	ICER vs. ST, $/QALY
DAPA + ST	44,594	6,562	5.151	0.592	11,092
ST	38,031		4.559		

DAPA + ST = dapagliflozin plus standard therapy; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; ST = standard therapy; vs. = versus.

Source: Sponsor's pharmacoeconomic submission.[3]

Deterministic analysis reported similar estimates of costs, QALYs, and ICER ($11,021).

Sensitivity and Scenario Analysis Results

Probabilistic scenario analyses were conducted, adopting different assumptions relating to discount rate (0% and 3%), time horizon (10 years), survival functions (Gompertz), patient demographics (Canadian), and a reduction in disutility associated with hospitalization (40%). Results were insensitive to these changes (ICER ranging from $10,991 to $12,929). A number of deterministic sensitivity analyses were also provided that included analysis by subgroups (T2DM and no T2DM; age ≤ 65 and age > 65; prior HHF and no prior HHF).

Results were insensitive, with the highest reported ICER of $14,176. No subgroup analysis was reported for NYHA class (II and III–IV), although the model has this feature.

In addition, the probabilistic scenario analysis comparing DAPA + ST to SAC-VAL + ST was conducted. In this analysis, DAPA + ST was dominant over SAC-VAL + ST in that DAPA + ST was associated with both lower costs and more QALYs.

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications for the economic analysis:

- **Lack of model transparency and flexibility:** CADTH identified that the spreadsheets that provide the number of patients in each health state for each cycle (the Markov trace) were not populated by formulas but were hard coded through macros. This severely restricts the transparency of the model, and CADTH requested that the model be revised to incorporate the actual formulas used to derive the Markov trace within the specific cells for each spreadsheet. The sponsor declined this request based on the argument that the model submitted was more efficient in terms of run time. CADTH proceeded to reproduce the submitted Markov model for ST but found the results diverged from the sponsor's. CADTH fully described the methods of their model and requested that the sponsor provide clear descriptions of the calculations required to estimate how individuals move between all health states for the first 10 cycles of the model to verify the reason for any discordance. The sponsor identified both an error in its model with respect to handling mortality, which it corrected, and a divergence in results, which occurred due to lack of transparency in the reporting of the sponsor's methods. The sponsor declined to provide the requested calculations. CADTH attempted to reproduce the submitted Markov model for DAPA + ST but again found that the results diverged from the sponsor's and requested that the sponsor provide the calculations for how individuals move between all health states for the first 10 cycles of the model to identify the reason for any discordance. The sponsor provided these calculations, and CADTH identified a further error in the sponsor's model with respect to the sponsor applying the hazard ratio for all-cause mortality to non-CV mortality.

  Applying the hazard ratio for all-cause mortality to non-CV mortality was not appropriate for 2 reasons. First, it would lead to the assumption that non-CV mortality for patients on DAPA + ST was lower than the Canadian average. Secondly, it involved applying a hazard ratio related to all-cause mortality to non-CV mortality, which is inappropriate as it is not the same population. This methodology was not clear within the sponsor's submitted report; therefore, the error was identified only by detailed reconstruction of the model. The sponsor's revised base-case analysis addressed this. There was a further error with respect to the data used to populate the survival functions. Again, this error was not transparent within the sponsor's submitted report and was identified only by detailed reconstruction of the model. The sponsor's revised base-case analysis addressed this.

  - Given the lack of transparency, the inflexibility of the model, and the numerous errors that were identified, CADTH expresses concern about whether all errors have been identified and resolved.

- **Results should be presented by NYHA class:** The full reports of the DAPA-HF trial suggest that DAPA + ST is [redacted] at study entry. As pre-specified in the CADTH Clinical Review protocol, NYHA classes were considered relevant subgroups of interest. Thus, based on the Canadian guidelines for economic evaluation, analysis should be stratified by NYHA class.

  - CADTH conducted stratified analyses by NYHA II and NYHA III–IV in reanalyses.

- **Treatment waning not explored:** Treatment efficacy is extrapolated from the 2-year trial data over the patient's life. The model does not allow the possibility of a treatment waning effect that is not captured within the 2-year trial period. Any significant waning effects that occur beyond 2 years may prevent long-term use of DAPA + ST from being cost-effective.
  - CADTH was unable to explore the impact of treatment waning due to the way in which the model was programmed.
- **Analysis should adopt class-specific mortality equations:** The submitted analysis adopted a set of adjusted mortality equations that assumed benefit with respect to reducing mortality in NYHA classes III and IV that is not evident in the clinical trial reports. The sponsor had stated in the submitted report [redacted]. In the clinical trial reports, the hazard ratio in patients in NYHA classes III and IV for CV and all-cause mortality for DAPA + ST versus ST was [redacted] and [redacted] respectively.
  - CADTH adopted the unadjusted mortality equations for NYHA classes III and IV provided in the submitted model, for which the hazard ratios were in line with the sponsor's clinical report.
- **Hospitalization time trend:** For HHF, the model assumes the rate of event increases with time. CADTH, in trying to replicate the model results, found a discordance in estimates of HHFs. This was explained by the sponsor as resulting from a capping of the increase in HHF at 29 months, as including the time trend beyond this would lead to very high rates of hospitalization. This was not detailed in the original or the revised report, and the lack of both statistical justification and validity for this approach suggests that an analysis without the time trend would be more valid.
  - The lack of flexibility within the model required CADTH to adopt unadjusted models for HHF, as the sponsor does in their base case. However, adopting the unadjusted equations is appropriate as it avoids the need to adopt a time trend with respect to this outcome.
- **Analysis should not assume improvement in terms of NYHA class:** The submitted model allowed patients to improve in terms of NYHA class. For NYHA classes II, III, and IV, patients were assumed to be more likely to improve in terms of their NYHA class than progress. For illustration, in the submitted analysis, if 1,000 patients started with DAPA + ST in NYHA class III, by 24 months, roughly 55 patients would be in NYHA class I, 378 in NYHA class II, 327 in NYHA class III, and 4 in NYHA class IV, and 236 would be dead. By 60 months, more patients would be in NYHA class I than III. The CADTH clinical expert indicated that this finding lacked face validity and that patients were unlikely in the long term to improve in terms of NYHA status.
  - CADTH wished to adopt the assumption of no improvements in NYHA status (Appendix 3, \Figure 2). However, it was not possible to adopt this assumption within the submitted model, as the probabilistic analysis returned an error when it was employed. CADTH therefore adopted the assumption that 0.01% of patients would move to an improved NYHA class and the balance of those previously assumed to improve would remain their current state. For example, for NYHA class III, the original probabilities within the model had 0.22% transitioning to NYHA class I, 3.17% to class II, 96.53% to class III, and 0.07% to class IV. The CADTH reanalysis assumed 0.01% to class I, 0.01% to class II, 99.91% to class III, and 0.07% to class IV.
- **Analysis should avoid double counting with respect to the costs of CV mortality and HHFs:** The sponsor included both the costs of HHFs and the costs associated with CV mortality. Given the likelihood that patients could be hospitalized prior to CV mortality, there is the potential for double counting by including both costs. In the sponsor's submitted base case, DAPA + ST was associated with a reduction in the costs of HHF of

$812 per patient and in costs associated with CV mortality of $287 compared to ST. The data pertaining to these costs came from an abstract that reports the costs of HHF with and without mortality.[15]

- To address this issue, CADTH adopted the cost from the abstract for all HHFs, $10,123 ($11,141 in 2020 Canadian dollars), but excluded the costs of CV mortality to avoid double counting.

- **Lack of validity within the comparison between DAPA + ST and SAC-VAL + ST:** Comparison between DAPA + ST and SAC-VAL + ST is based on a sponsor-conducted MAIC.[4] The CADTH Clinical Review states:

  The analysis had several limitations that threatened the internal validity of the results. Most notable were differences in the study design and populations enrolled in the 2 trials (such as the enrolment of an enriched population in the PARADIGM-HF study) and the derivation of patient weights independently for the active and control groups of the DAPA-HF study. The methods used to conduct the MAIC were not consistent with technical guidance and are of uncertain validity. As a result, no conclusions can be drawn from the indirect comparison.

  Thus, no comparison of cost-effectiveness can similarly be conducted.

  - CADTH did not report the results of DAPA + ST versus SAC-VAL + ST, and therefore the cost-effectiveness of DAPA + ST versus SAC-VAL + ST remains unknown.

- **Incorrect cost-effectiveness acceptability curves:** CADTH noted an error in the derivation of the cost-effectiveness acceptability curves. The data appear to be obtained by estimating the proportion of simulations where the ICER for DAPA + ST versus ST is below a specific threshold. This is inappropriate as it ignores the distribution of simulations across the different quadrants of the cost-effectiveness plane.[19] For example, a negative ICER could mean the drug increases costs but reduces health benefits or it could mean the drug reduces costs but increases health benefits. Thus, estimates of the probability that DAPA + ST is cost-effective for different threshold values of QALY will be incorrect.

  - CADTH was unable to address this limitation and therefore cautions against the probability of cost-effectiveness estimates used in the sponsor's analysis.

Additionally, further key assumptions were made by the sponsor and have been appraised by CADTH (see Table 4).

Table 4: Key Assumptions of the Submitted Economic Evaluation (Not Noted as Limitations to the Submission)

Sponsor's key assumption	CADTH comment
Use of utility values primarily from DAPA-HF	Appropriate
Costs of HF management, T2DM, HF visits, and adverse events from the literature	Appropriate
Assumption of continued benefit from DAPA + ST beyond the trial time horizon	Unclear if acceptable; not able to be tested with the submitted model

DAPA + ST = dapagliflozin plus standard therapy; HF = heart failure; T2DM = type 2 diabetes mellitus.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

The CADTH reanalysis was stratified by NYHA class (II and III–IV) and addressed the 3 limitations of the submitted model and report outlined above, namely, [redacted], patients should either remain in their current NYHA class or progress, and costs related to CV mortality and hospitalization should be changed to prevent double counting (Table 5).

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
1. Lack of reporting of results by NYHA class.	Sponsor-submitted model includes functionality to run analysis by NYHA class (II and III–IV) but does not report results.	CADTH used the functionality in the sponsor-submitted model to conduct analysis stratified by NYHA class as the base case (Table 6 and Appendix 3, Table 10).
Changes to derive the CADTH base case		
1. Adjusted mortality equations assumed a benefit of mortality in NYHA classes III and IV that is not evidenced in the unadjusted class-specific equations. Sponsor had stated that in the adjusted equations no mortality benefit is assumed in NYHA classes III and IV, but in the submitted model this was not the case.	Sponsor used adjusted equations relating to CV mortality, all-cause mortality and hospitalization for heart failure.	CADTH used the functionality in the sponsor-submitted model to adopt the unadjusted class-specific adjusted equations relating to CV mortality, all-cause mortality, and hospitalization for heart failure (Table 6 and Appendix 4, Table 15Table 14).
2. Improvement in NYHA state.	Sponsor assumed patients were more likely to improve to a better NYHA state each cycle than to progress.	CADTH assumed no improvements in NYHA state. For the probabilistic analysis to run without error, CADTH had to assume the probability that a patient transitioned to an improved NYHA state was 0.01% (Table 16and Appendix 4, Table 12).
3. There was a potential for double counting of costs associated with CV mortality.	The costs of heart failure hospitalizations and CV-related mortality were both included.	CADTH did not include the costs of CV-related mortality and included the average costs of all hospitalizations for heart failure (Table 17 and Appendix 4, Table 13).
CADTH base case		1+2+3

CV = cardiovascular; NYHA = New York Heart Association.

The CADTH base-case analysis stratified results by NYHA class, given the [redacted]. For patients in NYHA class II, the ICER for DAPA + ST versus ST alone was $8,760 (Table 6). DAPA + ST was associated with higher costs ($35,400 versus $26,037) and more QALYs (6.126 versus 5.057). Higher costs were again due to higher treatment costs and higher management costs, which were partially offset by reduced costs of HHF. The greater number of QALYs was due to increased life expectancy leading to greater time spent in NYHA classes II and III (Appendix 4, Table 18).

For patients in NYHA class III or IV, DAPA + ST was dominated by ST alone in that DAPA + ST was associated with higher costs ($28,923 versus $27,401) and fewer QALYs (3.670 versus 3.947) (Table 6). Higher costs were due to higher treatment costs, which were partially offset by reduced costs of HHF. The smaller number of QALYs was due [redacted] (Appendix 4, Table 18).

The reanalysis is based on the publicly available prices of the comparator treatments. Detailed results of the stepped analysis are provided in Appendix 4.

Given the error in the derivation of the cost-effectiveness acceptability curves, the model does not report a correct estimate of the probability of DAPA + ST being cost-effective at different willingness-to-pay thresholds for a QALY. Although the sponsor acknowledged the error, CADTH does not have access to the revised model and cannot provide a corrected value.

Table 6: Summary of the Stepped Analysis of the CADTH Reanalysis Results

		NYHA II			NYHA III and IV		
	Drug	Total costs, $	Total QALYs	ICER, $/QALY	Total costs, $	Total QALYs	ICER, $/QALY
Sponsor's corrected base case	ST	38,637	5.126		37,646	3.605	
	DAPA + ST	46,163	5.805	11,092	42,084	4.007	11,028
CADTH reanalysis 1	ST	38,614	5.125		41,122	4.202	
	DAPA + ST	47,290	6.220	7,922	42,856	3.902	DAPA + ST dominated by ST
CADTH reanalysis 2	ST	38,630	4.854		38,173	2.725	
	DAPA + ST	45,478	5.421	12,083	39,356	2.781	21,434
CADTH reanalysis 3	ST	25,959	5.126		24,175	3.605	
	DAPA + ST	33,753	5.805	11,488	28,694	4.007	11,228
CADTH base case (incorporates reanalyses 1, 2, and 3)	ST	26,037	5.057		27,401	3.947	
	DAPA + ST	35,400	6.126	8,760	28,923	3.670	DAPA + ST dominated by ST

DAPA + ST = dapagliflozin plus standard therapy; ICER = incremental cost-effectiveness ratio; NYHA = New York Heart Association; QALY = quality-adjusted life-year; ST = standard therapy.

Scenario Analysis Results

Given the favourable ICER for DAPA + ST versus ST alone in NYHA class II, price reduction analysis for this subgroup was not required.

For NYHA classes III and IV, the DAPA-HF trial suggested an [redacted] compared to ST; thus, DAPA + ST was dominated by ST based on this evidence.[5] Given the clinical data, for DAPA + ST in NYHA classes III and IV, price reductions of any level did not reduce the ICER below $50,000 per QALY.

Overall Conclusions

CADTH identified several concerns with the submitted model, which were addressed in a reanalysis. CADTH found that for patients in NYHA class II, the ICER for DAPA + ST versus ST was $8,760 per QALY. For patients in class III or IV, DAPA + ST was dominated by ST, meaning that DAPA + ST was more costly and associated with fewer QALYs. Thus, the CADTH reanalyses suggest that DAPA is likely cost-effective for the treatment of patients in NYHA II class but not cost-effective for those in NYHA class III or IV. Given [redacted], an ICER below $50,000 per QALY for DAPA + ST versus ST could not be achieved in any of CADTH's price reduction analyses.

CADTH's concerns regarding the lack of transparency and flexibility with the sponsor's submitted model remain. As such, the ability of CADTH to ensure the capture of all errors and the accuracy of the ICER estimate has been affected. Caution should be taken when considering the results from the sponsor's model.

Appendix 1: Cost Comparison Table

Table 7: CADTH Cost Comparison Table for Sodium-Glucose Cotransporter-2 Inhibitors Indicated for the Treatment of Heart Failure With Reduced Ejection Fraction

Treatment	Strength	Form	Price, $	Recommended dosage	Daily cost, $	Annual cost, $
Dapagliflozin (Forxiga)	5 mg 10 mg	Tablet	2.7300	10 mg once daily	2.73	996

Note: Prices are from Ontario Drug Benefit Formulary (June 2020) unless otherwise indicated.[14]

Table 8: CADTH Cost Comparison Table for Angiotensin-Converting Enzyme Inhibitors Indicated for the Treatment of Heart Failure

Treatment	Strength, mg	Form	Price, $	Recommended dosage	Daily cost, $	Annual cost, $
Captopril	6.25 12.5 25 50 100	Tablet	0.1237[a] 0.2120 0.3000 0.5590 1.0395	25 mg to 100 mg 3 times daily	0.90 to 3.12	329 to 1,138
Cilazapril	1 2.5 5	Tablet	0.3115 0.4295 0.4989	1 mg to 2.5 mg daily	0.31 to 0.43	114 to 157
Enalapril	2.5 5 10 20	Tablet	0.1863 0.2203 0.2647 0.3195	5 mg to 20 mg daily, 1 or 2 doses	0.22 to 0.32	80 to 193[b]
Fosinopril	10 20	Tablet	0.2178 0.2619	20 mg to 40 mg daily	0.26 to 0.52	96 to 191
Lisinopril	5 10 20	Tablet	0.1347 0.1619 0.1945	5 mg to 35 mg daily	0.13 to 0.49	49 to 179
Perindopril	2 4 8	Tablet	0.1632 0.2042 0.2831	2 mg to 4 mg daily	0.16 to 0.20	60 to 75
Quinapril	5 10 20	Tablet	0.4642	10 mg to 40 mg daily in 2 doses	0.46 to 0.93	169 to 339

Note: Dapagliflozin is specifically indicated for HF with reduced ejection fraction; the ACEIs are only indicated for HF. Ramipril is not specifically indicated for HF, but it is less expensive than other ACEIs, with an average annual cost ranging from $30 to $38.[14] Prices are from Ontario Drug Benefit Formulary (June 2020) unless otherwise indicated.[14]

[a] Saskatchewan Drug Benefit (June 2020).[20]

[b] Enalapril sometimes administered in 2 doses of 10 mg each; this price is based on the price for 10 mg pills twice daily.[21]

Table 9: CADTH Cost Comparison Table for Angiotensin Receptor Blockers Indicated for the Treatment of Heart Failure

Treatment	Strength, mg	Form	Price, $	Recommended dosage	Daily cost, $	Annual cost, $
Candesartan	4 8 16 32	Tablet	0.1700 0.2281 0.2281 0.2281	32 mg daily	0.23	83
Valsartan	80 160 320	Tablet	0.2159 0.2159 0.2098	80 mg to 160 mg twice daily	0.43	158

Note: Dapagliflozin is specifically indicated for HF with reduced ejection fraction; the ARBs are only indicated for HF.

Prices are from Ontario Drug Benefit Formulary (June 2020) unless otherwise indicated.[14]

Table 10: CADTH Cost Comparison Table for Beta-Blockers Indicated for the Treatment of Heart Failure

Treatment	Strength, mg	Form	Price, $	Recommended dosage	Daily cost, $	Annual cost, $
Carvedilol	3.125 6.25 12.5 25	Tablet	0.2431	3.125 mg to 25 mg twice daily	0.49	177

Note: Dapagliflozin is specifically indicated for HF with reduced ejection fraction; the beta-blocker is only indicated for HF. Atenolol and bisoprolol are not specifically indicated for HF, but they are less expensive than carvedilol, with an average annual cost ranging from $38 to $66.[14] Prices are from Ontario Drug Benefit Formulary (June 2020).[14]

Table 11: CADTH Cost Comparison Table for Other Treatments Indicated for the Treatment of Heart Failure[a]

Treatment	Strength, mg	Form	Price, $	Recommended dosage	Daily cost, $	Annual cost, $
Mineralocorticoid receptor antagonists						
Eplerenone	25 50	Tablet	2.0595	25 mg to 50 mg daily	2.06	752
Spironolactone	25 100	Tablet	0.0810 0.1910	25 mg to 200 mg daily	0.08 to 0.38	30 to 139
Other treatments indicated for HF[b]						
Sacubitril-valsartan (Entresto)	24/26 49/51 97/103	Tablet	3.7060	97 mg/103 mg twice daily	7.41	2,705
Bumetanide	1 5	Tablet	0.7907[c] 3.0184[c]	1 mg to 10 mg daily	0.79 to 6.04	289 to 2,203
Digoxin	0.0625 0.125 0.25	Tablet	0.2177 0.2060 0.2060	0.0625 mg to 0.25 mg daily	0.21 to 0.22	75 to 79
Furosemide	20 40 80	Tablet	0.0219 0.0327 0.0703[c]	40 mg to 80 mg daily	0.03 to 0.07	12 to 26
Ivabradine	5 7.5	Tablet	0.8709 1.5942	5 mg to 7.5 mg twice daily	1.74 to 3.19	636 to 1,164

HF = heart failure.

[a] Treatments recommended by the *Canadian Journal of Cardiology* or suggested by e-Therapeutics.[1,22]

[b] Sacubitril-valsartan (Entresto), digoxin, and ivabradine are indicated for HF with reduced ejection fraction.[23-25]

[c] From Saskatchewan formulary.[20]

Prices are from Ontario Drug Benefit Formulary (June 2020) unless otherwise indicated.[14]

Appendix 2: Submission Quality

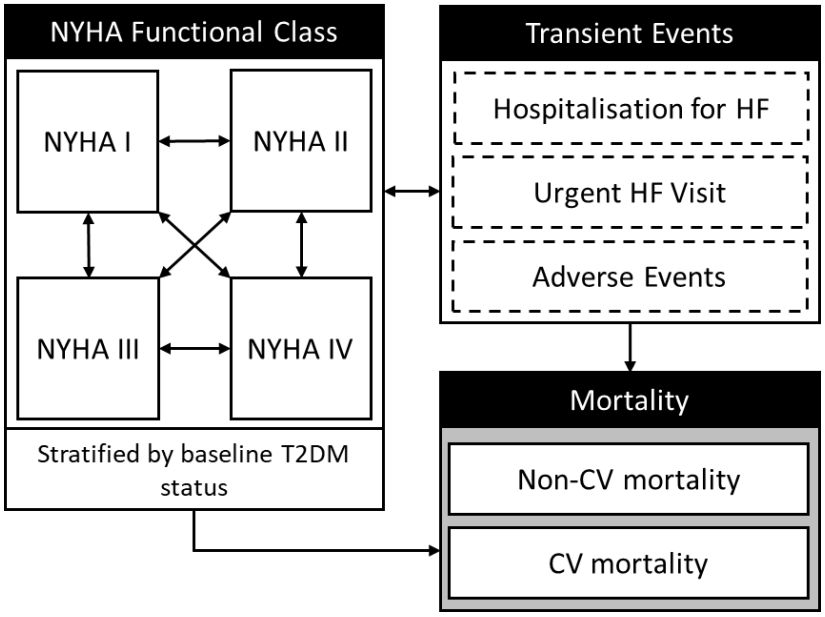
Table 12: Submission Quality

Description	Yes	No	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing	☐	☒	Stratified analysis by NYHA class should have been provided as the base case.
Model has been adequately programmed and has sufficient face validity	☐	☒	The model was inappropriately programmed and had limited face validity. There were serious concerns with the lack of transparency with both the model and its reporting. The hard-coding of the model seriously restricted the ability of CADTH to validate the model. CADTH identified 3 errors with the original submitted analysis. Given the lack of transparency, CADTH cannot be certain that all errors in the model have been identified.
Model structure is adequate for decision problem	☒	☐	
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	☒	☐	
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	☐	☒	The lack of stratified analysis by NYHA class led to the analysis presented being inappropriate for the decision problem. There was lack of flexibility in conducting analyses by functional form as the user could only adopt the same functional form for all survival curves. There was lack of flexibility in choosing between unadjusted and adjusted equations.
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details)	☐	☒	There were errors in reporting with respect to mortality equations and a lack of adequate technical documentation relating to the model.

NYHA = New York Heart Association.

Appendix 3: Additional Information on the Submitted Economic Evaluation

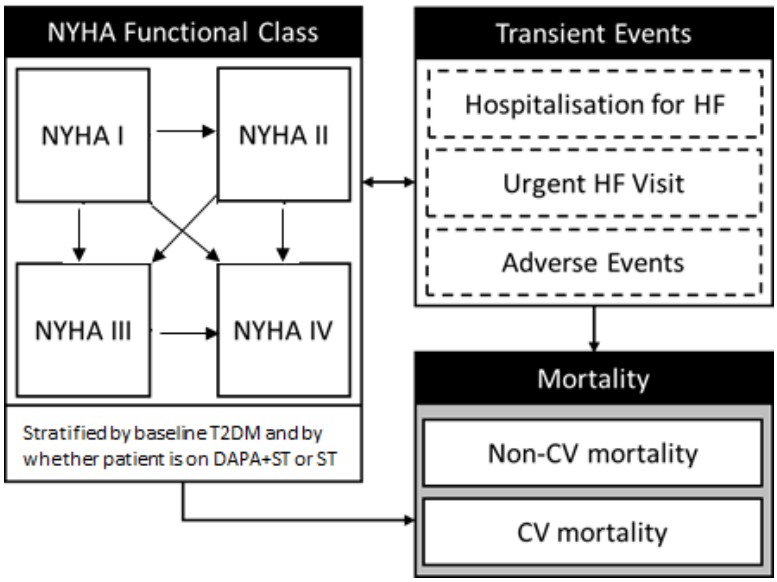
Figure 1: Sponsor's Representation of Submitted Model's Structure



CV = cardiovascular; HF = heart failure; NYHA = New York Heart Association; T2DM = type 2 diabetes mellitus.

Source: Sponsor's pharmacoeconomic submission.[3]

Figure 2: Appropriate Model Structure That CADTH Would Have Preferred to Adopt in the Base Case



CV = cardiovascular; DAPA = dapagliflozin; HF = heart failure; NYHA = New York Heart Association; ST = standard therapy; T2DM = type 2 diabetes mellitus.

Source: Edited sponsor's pharmacoeconomic submission.[3]

Detailed Results of the Sponsor's Base Case

Table 13 details the disaggregated results of the sponsor's base case. Note that the majority of QALY gains occur in NYHA classes I and II.

Table 13: Disaggregated Summary of Sponsor's Base Case

Parameter	DAPA + ST	ST	Incremental	Percentage (of total incremental)
Discounted life-years				
Life expectancy	6.932	6.148	0.784	
Discounted QALYs				
NYHA I	0.917	0.766	0.150	25.4
NYHA II	3.612	3.205	0.407	68.8
NYHA III	0.631	0.599	0.032	5.4
NYHA IV	0.018	0.017	0.001	0.2
Hospitalization	–0.021	–0.023	0.002	0.4
Urgent HF visit	0.000	0.000	0.000	0.0
Adverse events	–0.006	–0.005	–0.001	0.0
Total	5.151	4.559	0.592	
Discounted costs, $				
Treatment costs (intervention)	10,803	4,268	6,535	99.6
Background medical management	7,571	6,691	881	13.4
Hospitalization for HF	7,884	8,696	–812	–12.4
Urgent HF visit	23	39	–16	–0.2
CV-specific mortality	13,497	13,784	–287	–4.4
Adverse event costs	4,815	4,553	261	4.0
Total	44,594	38,031	6,562	

CV = cardiovascular; DAPA = dapagliflozin; HF = heart failure; NYHA = New York Heart Association; QALY = quality-adjusted life-year; ST = standard therapy.

Table 14 details the disaggregated results stratified by NYHA class based on the sponsor's submitted model. Patients who start the model in NYHA classes III and IV spend more time in the health states relating to NYHA classes I and II. Furthermore, for patients in NYHA classes III and IV, the majority of QALY gains come from more time spent in NYHA classes I and II for patients on DAPA + ST. Finally, NYHA class II and IV patients on DAPA + ST have longer life expectancies than those on ST alone, contrary to what might be expected given the results of the DAPA-HF clinical trial.

Table 14: Disaggregated Summary of Analysis Stratified by NYHA Class From Sponsor's Submitted Model

	NYHA class II			NYHA class III and IV		
Parameter	**DAPA + ST**	**ST**	**Incremental**	**DAPA + ST**	**ST**	**Incremental**
Discounted life-years						
Life expectancy	7.746	6.846	0.900	5.508	4.977	0.531
Discounted QALYs						
NYHA I	1.113	0.939	0.175	0.588	0.488	0.100
NYHA II	4.390	3.924	0.466	2.173	1.900	0.273
NYHA III	0.318	0.283	0.035	1.240	1.215	0.025
NYHA IV	0.010	0.009	0.001	0.034	0.033	0.001
Hospitalization	–0.020	–0.021	0.002	–0.023	–0.027	0.004
Urgent HF visit	0.000	0.000	0.000	0.000	0.000	0.000
Adverse events	–0.006	–0.006	–0.001	–0.005	–0.004	0.000
Total	5.805	5.126	0.678	4.007	3.605	0.402
Discounted costs, $						
Treatment costs (intervention)	11,902	4,753	7,148	8,787	3,456	5,332
Medical management	8,186	7,202	985	6,530	5,894	636
Hospitalization for HF	7,555	8,135	–580	8,722	10,146	–1,423
Urgent HF visit	27	44	–17	18	32	–14
CV-specific mortality	13,148	13,474	–326	14,242	14,462	–219
Adverse event costs	5,345	5,030	315	3,784	3,657	127
Total	46,163	38,637	7,526	42,084	37,646	4,439

CV = cardiovascular; DAPA = dapagliflozin; HF = heart failure; NYHA = New York Heart Association; QALY = quality-adjusted life-year; ST = standard therapy.

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Table 15 to Table 18 provide a detailed breakdown of CADTH's stepped reanalysis by NYHA class.

Table 15: Disaggregated Summary of CADTH's Reanalysis: [redacted]

	NYHA class II			NYHA class III and IV		
Parameter	**DAPA + ST**	**ST**	**Incremental**	**DAPA + ST**	**ST**	**Incremental**
Discounted life-years						
Life expectancy	8.307	6.850	1.457	5.387	5.796	–0.410
Discounted QALYs						
NYHA I	1.195	0.923	0.272	0.525	0.588	–0.063
NYHA II	4.642	3.903	0.739	2.039	2.230	–0.191
NYHA III	0.396	0.316	0.081	1.330	1.380	–0.050
NYHA IV	0.012	0.010	0.002	0.036	0.038	–0.001
Hospitalization	–0.018	–0.020	0.002	–0.024	–0.028	0.004
Urgent HF visit	0.000	0.000	0.000	0.000	0.000	0.000
Adverse events	–0.007	–0.006	–0.001	–0.004	–0.005	0.000
Total	6.220	5.125	1.095	3.902	4.202	–0.300
Discounted costs, $						
Treatment costs (intervention)	12,782	4,756	8,026	8,411	4,024	4,387
Medical management	9,378	7,731	1,647	6,865	7,386	–521
Hospitalization for HF	6,801	7,737	–936	9,073	10,706	–1,632
Urgent HF visit	29	43	–15	18	37	–18
CV-specific mortality	12,543	13,293	–750	14,761	14,692	69
Adverse event costs	5,758	5,055	703	3,727	4,278	–551
Total	47,290	38,614	8,676	42,856	41,122	1,734

CV = cardiovascular; DAPA = dapagliflozin; HF = heart failure; NYHA = New York Heart Association; QALY = quality-adjusted life-year; ST = standard therapy.

Table 16: Disaggregated Summary of CADTH's Reanalysis: Limited Improvement in NYHA Class

	NYHA class II			NYHA class III and IV		
Parameter	**DAPA + ST**	**ST**	**Incremental**	**DAPA + ST**	**ST**	**Incremental**
Discounted life-years						
Life expectancy	7.307	6.548	0.759	4.093	4.023	0.070
Discounted QALYs						
NYHA I	0.021	0.018	0.003	0.011	0.010	0.001
NYHA II	4.581	4.111	0.470	0.024	0.020	0.003
NYHA III	0.789	0.703	0.086	2.622	2.581	0.041
NYHA IV	0.057	0.050	0.006	0.154	0.151	0.003
Hospitalization	–0.021	–0.023	0.002	–0.027	–0.033	0.007
Urgent HF visit	0.000	0.000	0.000	0.000	0.000	0.000

	NYHA class II			NYHA class III and IV		
Parameter	**DAPA + ST**	**ST**	**Incremental**	**DAPA + ST**	**ST**	**Incremental**
Adverse events	–0.006	–0.005	–0.001	–0.003	–0.003	0.000
Total	5.421	4.854	0.567	2.781	2.725	0.055
Discounted costs, $						
Treatment costs (intervention)	11,341	4,546	6,795	6,753	2,793	3,960
Medical management	7,699	6,867	832	4,833	4,753	80
Hospitalization for HF	8,017	8,749	–732	10,086	12,652	–2,566
Urgent HF visit	25	42	–17	13	26	–13
CV-specific mortality	13,350	13,606	–256	14,865	14,986	–121
Adverse event costs	5,046	4,821	226	2,806	2,963	–156
Total	45,478	38,630	6,847	39,356	38,173	1,183

CV = cardiovascular; DAPA = dapagliflozin; HF = heart failure; NYHA = New York Heart Association; QALY = quality-adjusted life-year; ST = standard therapy.

Table 17: Disaggregated Summary of CADTH's Reanalysis: Avoidance of Double Counting

	NYHA class II			NYHA class III and IV		
Parameter	**DAPA + ST**	**ST**	**Incremental**	**DAPA + ST**	**ST**	**Incremental**
Discounted life-years						
Life expectancy	7.746	6.846	0.900	5.508	4.977	0.531
Discounted QALYs						
NYHA I	1.113	0.939	0.175	0.588	0.488	0.100
NYHA II	4.390	3.924	0.466	2.173	1.900	0.273
NYHA III	0.318	0.283	0.035	1.240	1.215	0.025
NYHA IV	0.010	0.009	0.001	0.034	0.033	0.001
Hospitalization	–0.020	–0.021	0.002	–0.023	–0.027	0.004
Urgent HF visit	0.000	0.000	0.000	0.000	0.000	0.000
Adverse events	–0.006	–0.006	–0.001	–0.005	–0.004	0.000
Total	5.805	5.126	0.678	4.007	3.605	0.402
Discounted costs, $						
Treatment costs (intervention)	11,902	4,753	7,148	8,787	3,456	5,332
Medical management	8,293	8,930	–637	6,530	5,894	636
Hospitalization for HF	7,555	8,135	–580	9,575	11,137	–1,562
Urgent HF visit	27	44	–17	18	32	–14
CV-specific mortality	0	0	0	0	0	0
Adverse event costs	5,345	5,030	315	3,784	3,657	127
Total	33,753	25,959	7,795	28,694	24,175	4,519

CV = cardiovascular; DAPA = dapagliflozin; HF = heart failure; NYHA = New York Heart Association; QALY = quality-adjusted life-year; ST = standard therapy.

Table 18 provides the breakdown of results for CADTH's base-case analysis. For both strata, patients spent the majority of time in their starting health state, with few patients showing improvement in their NYHA class. Also, analysis by NYHA classes III and IV was more consistent with the results of the DAPA-HF clinical trial.

Table 18: Disaggregated Summary of CADTH's Reanalysis: Base Case

	NYHA class II			NYHA class III and IV		
Parameter	**DAPA + ST**	**ST**	**Incremental**	**DAPA + ST**	**ST**	**Incremental**
Discounted life-years						
Life expectancy	8.310	6.850	1.460	5.386	5.796	–0.411
Discounted QALYs						
NYHA I	0.024	0.018	0.006	0.013	0.014	–0.001
NYHA II	4.721	4.034	0.687	0.027	0.030	–0.004
NYHA III	1.292	0.952	0.340	3.419	3.670	–0.251
NYHA IV	0.113	0.079	0.035	0.240	0.266	–0.026
Hospitalization	–0.018	–0.020	0.002	–0.024	–0.028	0.004
Urgent HF visit	0.000	0.000	0.000	0.000	0.000	0.000
Adverse events	–0.007	–0.006	–0.001	–0.004	–0.005	0.000
Total	6.126	5.057	1.069	3.670	3.947	–0.277
Discounted costs, $						
Treatment costs (intervention)	12,798	4,756	8,042	8,423	4,024	4,399
Medical management	9,391	7,743	1,649	6,864	7,388	–524
Hospitalization for HF	7,412	8,431	–1,019	9,885	11,667	–1,782
Urgent HF visit	28	43	–15	18	36	–18
CV-specific mortality	0	0	0	0	0	0
Adverse event costs	5,771	5,064	706	3,733	4,285	–552
Total	35,400	26,037	9,364	28,923	27,401	1,522

CV = cardiovascular; DAPA = dapagliflozin; HF = heart failure; NYHA = New York Heart Association; QALY = quality-adjusted life-year; ST = standard therapy.

Appendix 5: Submitted Budget Impact Analysis and CADTH Appraisal

Key Take-Aways of the Budget Impact Analysis

- CADTH identified the following key limitations with the sponsor's analysis:
  - Assuming that a proportion of the uptake of dapagliflozin will come from patients switching from sacubitril-valsartan was deemed inappropriate by clinical experts consulted by CADTH.
  - Restricting use to patients in NYHA classes II to IV was considered uncertain, as this is not specified in dapagliflozin's heart failure indication, and there is heterogeneity in assessing NYHA class.
  - The uptake of dapagliflozin was considered uncertain.
- The CADTH reanalyses included assuming that 100% of the uptake of dapagliflozin comes from adding on to standard of care and assuming that no patients will switch from sacubitril-valsartan.
- Based on the CADTH reanalyses, the budget impact from the introduction of dapagliflozin is expected to be $3,342,910 in year 1, $10,479,952 in year 2, and $14,911,691 in year 3, with a 3-year total budget impact of $28,734,553. Uncertainty remains regarding prescribing practices by NYHA class, along with the forecasted uptake of dapagliflozin.

NYHA = New York Heart Association.

Summary of Sponsor's Budget Impact Analysis

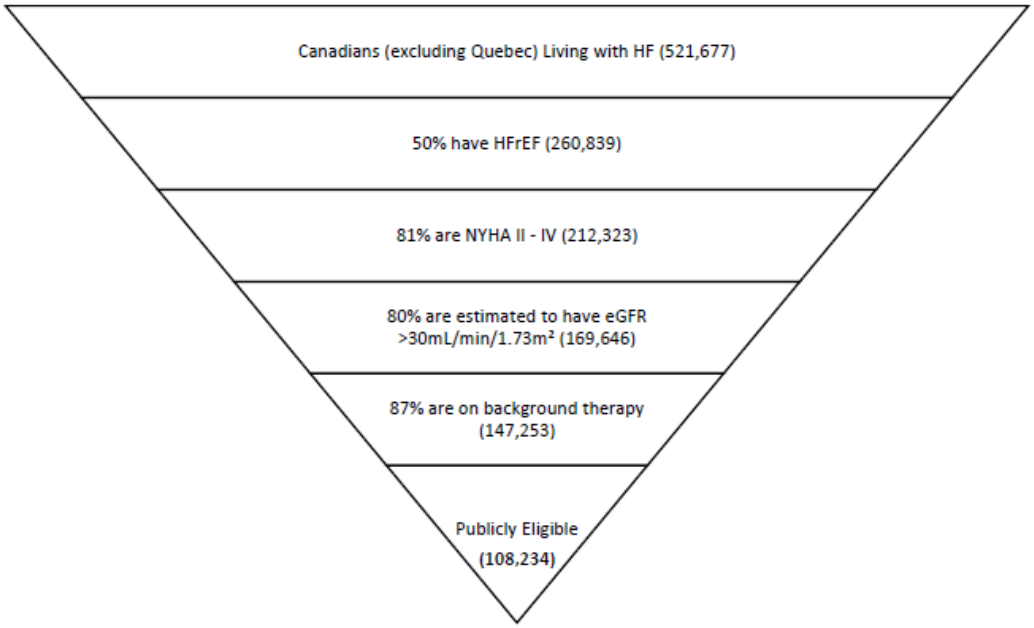
The sponsor submitted a budget impact analysis (BIA) estimating the incremental budget impact of reimbursing DAPA for the treatment of patients with HFrEF. The BIA was undertaken from a publicly funded drug plan perspective that considered only drug costs in the base-case analysis. The analytic framework, which used an epidemiology-based approach, leveraged data from multiple sources in the literature and assumptions based on clinical expert input to determine the estimated population size (Figure 3). New patients were added to the BIA via an annual population growth rate. The population was stratified by patients with T2DM, which was 40.5% based on the QUALIFY patient registry.[26]

The sponsor compared a reference scenario in which DAPA was not reimbursed for HFrEF with a new drug scenario, in which DAPA was funded as per the proposed Health Canada indication. The reference scenario stratified the target population by currently available treatment options, which included standard of care alone; SAC-VAL with a beta-blocker and an MRA; and empagliflozin or canagliflozin with standard of care. Standard of care consisted of an ACEI or ARB, a beta-blocker, and an MRA. Empagliflozin and canagliflozin were included in the reference scenario as it was expected that some patients with concomitant heart failure and T2DM would be receiving a sodium-glucose cotransporter-2 (SGLT2) inhibitor. In the reference scenario, SGLT2 inhibitors are only reimbursed for T2DM. Shares of the SGLT2 inhibitors and SAC-VAL were based on IQVIA PharmaStat data, while the remainder of the market shares were assumed to be standard of care alone.

The new drug scenario consisted of 3 sources of uptake for DAPA: DAPA as an add-on to standard of care; DAPA used instead of SAC-VAL; and a switch to DAPA from empagliflozin or canagliflozin. The size of DAPA's estimated market share is provided in Table 19 and was based on the sponsor's internal forecasting estimates. The sponsor assumed that all uptake would occur in HFrEF patients without T2DM (i.e., patients currently receiving other SGLT2 inhibitors would not switch to DAPA), except for in British Columbia, where DAPA is not currently funded for T2DM. The sponsor assumed that the majority of the uptake of DAPA would consist of add-on to standard of care. However, a proportion (10% in year 1, 15% in year 2, and 20% in year 3) would switch from SAC-VAL to DAPA.

Drug costs were inclusive of markups and dispensing fees. Standard of care costs included a weighted cost for ACEIs and ARBs based on the proportions observed in the DAPA-HF trial.

Figure 3: Sponsor's Estimation of the Size of the Eligible Population



eGFR: estimated glomerular filtration rate; HF: heart failure; HFrEF: heat failure with reduced ejection fraction; NYHA: New York Heart Association.

Source: Sponsor's budget impact analysis submission.[3]

Table 19: Summary of Key Model Parameters

Parameter	Sponsor's estimate (reported as year 1, year 2, and year 3, if appropriate)
Target population	
Number of patients eligible for drug under review	112,152 / 116,217 / 120,433
Market uptake (3 years), %	
Uptake (reference scenario)[a] Dapagliflozin + SOC[b] HF, no T2DM HF + T2DM SOC Sacubitril-valsartan + BB + MRA Empagliflozin or canagliflozin + SOC	 2.2 / 2.3 / 2.3 0.0 / 0.0 / 0.0 2.2 / 2.3 / 2.3 81.2 / 79.9 / 79.2 4.6 / 5.5 / 6.0 12.0 / 12.3 / 12.5
Uptake (new drug scenario)[a] Dapagliflozin + SOC HF, no T2DM HF + T2DM SOC Sacubitril-valsartan + BB + MRA Empagliflozin or canagliflozin + SOC	 6.3 / 15.1 / 20.0 4.0 / 12.9 / 17.9 2.2 / 2.3 / 2.3 77.6 / 69.0 / 64.8 4.1 / 3.6 / 2.4 12.0 / 12.3 / 12.5

Parameter	Sponsor's estimate (reported as year 1, year 2, and year 3, if appropriate)
Cost of treatment per patient, $	
Cost of treatment over 1 year[c]	
Dapagliflozin + SOC	1,867
SOC	694
Sacubitril-valsartan + BB + MRA	3,269
Empagliflozin or canagliflozin + SOC	1,898

BB = beta-blocker; HF = heart failure; MRA = mineralocorticoid receptor antagonist; SOC = standard of care; T2DM = type 2 diabetes mellitus.

Market shares were presented by the sponsor by jurisdiction only; therefore, pan-Canadian market shares in the reference and new drug scenarios were not provided. The market shares presented are for Ontario.

[b] In the reference scenario, only patients who have T2DM receive dapagliflozin as indicated for their T2DM.

[c] Costs presented are for Ontario, using costs from the Ontario Drug Benefit Formulary.[14]

Summary of the Sponsor's BIA Results

The sponsor estimated the net budget impact of introducing DAPA for HFrEF, including standard of care costs, to be $2,477,616 in year 1, $6,176,952 in year 2, and $6,661,273 in year 3, for a total budget impact over 3 years of $15,315,842.

CADTH Appraisal of the Sponsor's BIA

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA:

- **Assuming that existing patients will switch from SAC-VAL to DAPA is inappropriate.** In the sponsor's new drug scenario, it was assumed that 10%, 15%, and 20% of the uptake of DAPA in years 1, 2, and 3, respectively, would come from patients switching from SAC-VAL to DAPA. The remaining uptake would come from DAPA as an add-on to standard of care. According to clinical experts consulted by CADTH for this review, it is unlikely that patients currently taking SAC-VAL would switch to DAPA, as was assumed by the sponsor.
  - In CADTH reanalyses, it was assumed that 100% of the uptake of DAPA comes from an add-on to standard of care, and no patients would switch from SAC-VAL. CADTH also explored a scenario analysis that assumed a percentage of new patients would initiate DAPA rather than SAC-VAL.
- **Uncertainty regarding whether DAPA will be initiated in NYHA class I.** In the sponsor's BIA, only symptomatic (NYHA class II to IV) patients received DAPA, which is aligned with the inclusion criteria observed in the DAPA-HF trial.[5] However, according to the product monograph for DAPA, the CV indication does not specify that patients must be in NYHA class II or symptomatic.[27] Additionally, clinical experts consulted by CADTH noted heterogeneity in assessing NYHA class, and therefore might prescribe DAPA for patients with NYHA class I.
  - As uncertainty remains regarding physician prescribing practices, CADTH explored including NYHA class I patients in the BIA as a scenario analysis.
- **Uncertainty regarding uptake of DAPA.** The sponsor assumed that 4%, 12.9%, and 17.9% of eligible patients would receive DAPA in years 1, 2, and 3, respectively, based on internal forecasting estimates.[3] Clinical experts consulted by CADTH noted that this rate of uptake might be optimistic. If uptake is less than forecasted by the sponsor, this will decrease the 3-year budget impact of reimbursing DAPA.

Additional limitations were identified but were not considered to be key limitations. These limitations include using the number of prevalent heart failure patients from 2012–2013, rather than applying the prevalence rate to current population statistics, and not accounting for new (incident) cases diagnosed with HFrEF over the model time horizon.

CADTH Reanalyses of the BIA

CADTH revised the sponsor's submission by assuming that 100% of the uptake of DAPA would come as an add-on to standard of care, and no patients will switch from SAC-VAL. The assumptions used by the sponsor in comparison to those used by CADTH in its reanalysis are available in Table 20.

Table 20: Changes to derive the CADTH base case

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case (none)		
Changes to derive the CADTH base case		
Source of uptake of dapagliflozin (CADTH base case)	90% / 85% / 80% as add-on to SOC for years 1, 2 and 3 respectively 10% / 15% / 20% as a switch from sacubitril-valsartan for years 1, 2 and 3 respecitively	100% as add-on to SOC No switching from sacubitril-valsartan

BIA = budget impact analysis; SOC = standard of care.

Applying these changes increased the 3-year total costs to $28,734,553. As DAPA is less costly than SAC-VAL, having some patients switching to DAPA from SAC-VAL introduced cost savings in the analysis. Therefore, removing this assumption and assuming all uptake comes from add-on to standard of care increases the budget impact of introducing DAPA. The results of the CADTH reanalysis are presented in summary format in Table 21, and a more detailed breakdown is presented in Table 22.

Table 21: Summary of the CADTH Reanalyses of the BIA

Stepped analysis	Three-year total, $
Submitted base case	15,315,842
CADTH base case	28,734,553

BIA = budget impact analysis.

Note: The submitted analysis is based on the publicly available prices of the comparator treatments.

CADTH also conducted additional scenario analyses to address remaining uncertainty:

- Assumed that 10%, 15%, and 20% of new patients added to the BIA would initiate DAPA rather than SAC-VAL each year by multiplying these values by the jurisdiction's population growth rate.
- Assumed patients would be eligible for DAPA regardless of NYHA class (i.e., including NYHA class I patients).
- Assumed only NYHA class II patients would be eligible for DAPA (60.5% of heart failure patients).[26]

The results of CADTH's scenario analyses demonstrate that assuming a proportion of new patients will initiate DAPA rather than SAC-VAL has a negligible influence on model results (Table 22). Assuming all patients would be eligible for DAPA regardless of NYHA class

increases the budget impact to $35,300,434, while restricting DAPA to only NYHA class II patients decreases the impact to $21,356,762.

Table 22: Detailed Breakdown of the CADTH Reanalyses of the BIA

Stepped analysis	Scenario	Year 0 (current situation), $	Year 1, $	Year 2, $	Year 3, $	Three-year total, $
Submitted base case	Reference	106,146,913	113,252,227	120,519,835	127,144,303	360,916,364
	New drug	106,146,913	115,729,843	126,696,787	133,805,576	376,232,206
	Budget impact	**0**	**2,477,616**	**6,176,952**	**6,661,273**	**15,315,842**
CADTH base case	Reference	106,146,913	113,252,227	120,519,835	127,144,303	360,916,364
	New drug	106,146,913	116,595,137	130,999,787	142,055,994	389,650,917
	Budget impact	**0**	**3,342,910**	**10,479,952**	**14,911,691**	**28,734,553**
CADTH scenario analysis 1: Percentage of new patients initiate dapagliflozin rather than sacubitril-valsartan	Reference	106,146,913	113,252,227	120,519,835	127,144,303	360,916,364
	New drug	106,146,913	116,564,191	130,845,900	141,760,938	389,171,028
	Budget impact	**0**	**3,311,964**	**10,326,065**	**14,616,635**	**28,254,664**
CADTH scenario analysis 2: Patients treated regardless of NYHA class (i.e., 100% of NYHA class I to IV)	Reference	130,401,613	139,130,500	148,058,765	156,196,932	443,386,197
	New drug	130,401,613	143,237,269	160,933,399	174,515,963	478,686,631
	Budget impact	**0**	**4,106,769**	**12,874,634**	**18,319,030**	**35,300,434**
CADTH scenario analysis 3: Only NYHA class II treated (60.5%)	Reference	78,892,976	84,173,952	89,575,553	94,499,144	268,248,649
	New drug	78,892,976	86,658,548	97,364,707	105,582,157	289,605,412
	Budget impact	**0**	**2,484,595**	**7,789,154**	**11,083,013**	**21,356,762**

BIA = budget impact analysis; NYHA = New York Heart Association.

Note: The submitted analysis is based on the publicly available prices of the comparator treatments.

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