Heart Failure Related Outcomes in Patients within a Specialized Clinic-Based Cohort and a Population Level Cohort: Emphasis on Diabetes

Luke Gagnon

A Thesis in partial fulfilment of the requirements for the degree of

Master of Science

In

Translational Medicine

Department of Medicine

University of Alberta

Abstract

Diabetes mellitus (DM) is a well-established risk factor for adverse prognosis in patients with heart failure (HF). Outcomes in this patient population have not been thoroughly investigated in specialized heart function clinics (HFC). Recently, sodium-glucose cotransporter-2 (SGLT2) inhibitors have become a novel treatment for patients with HF. In addition to the natriuretic effect of SGLT2 inhibitors they likely have direct positive effects on the heart, proving to be efficacious in adults with HF based on randomized clinical trials.

We aim to assess the initiation of SGLT2 inhibitors in HF patients with and without DM to assess utilization of this novel medication, as well as investigate more thoroughly the difference in HF patients with and without DM. We investigated outcomes of DM patients in a specialized HFC and compared to patients without DM, and their guideline-directed medical therapy (GDMT) utilization. Additionally, we compared SGLT2 inhibitor uptake and outcomes in two real-world cohorts: a population-based cohort of all adults with DM and HF in Alberta, Canada and a HFC cohort. The HFC cohort was created by chart review of patients seen in the HFC between February 2018 and August 2022. We examined GDMT utilization, baseline reported quality of life and outcomes amongst DM and non-DM cohort. The population-based cohort was derived from linked provincial healthcare datasets. We examined the association between SGLT2 inhibitor use (modeled as a time-varying covariate) and all-cause mortality or deaths/cardiovascular hospitalizations.

Of the 4,885 individuals with DM and HF in the population-based cohort, 64.2% met the eligibility criteria of the trials proving the efficacy of SGLT2 inhibitors, SGLT2 inhibitor usage

increased from 1.2% in 2017 to 26.4% by January 2022. In comparison, of the 530 patients with DM and HF followed in the HFC, SGLT2 inhibitor use increased from 9.8% in 2019 to 49.1 % by March 2022. SGLT2 inhibitor use in the population-based cohort was associated with fewer deaths (aHR 0.51, 95% CI 0.41–0.63) and fewer deaths/cardiovascular hospitalizations (aHR 0.65, 95% CI 0.54–0.77). SGLT2 inhibitor usage rates were far lower in HF patients without DM (3.5% by March 2022 in the HFC cohort).

Within the HFC, patients with DM had higher rates of co-morbidities with the largest differences seen in hypertension (70.6% vs 43.8%), dyslipidemia (32.8% vs 16.9%) and chronic kidney disease (44.7% vs 26.1%), compared to those without DM (all p values < 0.001). Additionally, it was more common for patients with DM to have HF secondary to ischemic heart disease ($p < 0.001$). Patients without DM were more likely to have heart failure with preserved ejection fraction (HFpEF) compared to those with DM ($p < 0.05$). The main significant difference in GDMT utilization was SGLT2 inhibitor usage across all HF sub-types, which was much higher in the DM group (DM group = 33.8% vs. non-DM group = 3.1%, $p < 0.001$). In the heart failure with reduced ejection fraction (HFrEF) group for the overall cohort, GDMT utilization was 17.9% for SGLT2 inhibitors, 96.5% for beta-blocker, 82.0% for mineral corticoid receptor antagonists (MRA), and 94.6% for renin-angiotensin system (RAS) inhibitors. Additionally, In the HFrEF group for the overall cohort, 81.0% were on triple therapy and 16.0% on quadruple therapy. Patient-reported QoL was worse in those with DM (median 68.1, IQR: 45.8 – 87.5) compared to those without DM (76.0, IQR: 53.1 – 92.7, $p < 0.001$). When comparing patients based on ejection fraction only, QoL was significantly better in the heart failure with preserved ejection fraction (HFpEF) group compared to HFrEF and heart failure mildly reduced ejection fraction (HFmrEF)

patients ($p < 0.001$). During a median follow-up time of 38.7 months (IQR: 30.7 – 48.2 months), patients with DM exhibited an increased risk of composite outcomes (aHR: 1.34, 95% CI 1.13 – 1.60) and all-cause mortality alone (aHR: 1.12, 95% CI 1.01 – 1.43) compared to non-DM patients.

Our results critically highlight that HF patients with DM are a complex and vulnerable patient population, and special consideration for follow-up, management of comorbidities and rapid initiation of SGLT2 inhibitors should be given.

Preface

This thesis is an original work by Luke Gagnon. All included research received research ethics approval from the University of Alberta (Pro00077124 and Pro00010852).

A portion of this study has been published as "Uptake of SGLT2i and Outcomes in Patients with Diabetes and Heart Failure: A Population-Based Cohort and a Specialized Clinic Cohort, Luke R. Gagnon, Deepan Hazra, Kevin Perera, Kaiming Wang, Chandu Sadasivan, Erik Youngson, Luan Chu, Douglas C. Dover, Padma Kaul, Scot Simpson, Aminu Bello, Finlay A. McAlister, Gavin Y. Oudit" in the American Heart Journal (https://doi.org/10.1016/j.ahj.2024.04.007)[1].

For the data involving the Heart function Clinic, I participated in numerous patient consents, countless amounts of data collection and chart review and utilized the assistance of the abSPOR group for confirming data and obtaining outcome data. I completed the statistical analysis independently. Additionally, I have spent time in a clinical capacity in the Heart Function Clinic to experience first-hand the impact this clinic has on patients.

The population level data was obtained and analysed through the assistance of the VIGOUR group.

This study is based in part on data provided by Alberta Health and Alberta Health Services to the Alberta Strategy for Patient Oriented Research Support Unit (which receives infrastructure funding from CIHR, Alberta Innovates, and the University Hospital Foundation). The

interpretation and conclusions contained herein are those of the researchers and do not represent the views of the Government of Alberta nor Alberta Health Services. Neither the Government of Alberta nor Alberta Health Services express any opinion in relation to this study.

Acknowledgement

I would like to thank my supervisor, Dr. Gavin Oudit, for his mentorship and support through many years of our clinical and research relationship. I would also like to thank the core Internal Medicine program and the program director at the time, Dr. Steven Katz, for their support during my residency to pursue this Masters and providing me with research rotations to help complete my research endeavours. I would also like to thank Dr. Finlay McAlister and Dr. Scot Simpson as co-supervisors, Dr. Dean Eurich as the external examiner, as well as Dr. Chandu Sadasivan and Mr. Kaiming (Billy) Wang as members of the same laboratory for providing ongoing research mentorship.

We would like to acknowledge and thank the patients and their families for their involvement in this study and the multi-disciplinary team at the Heart Function Clinic for their support and valuable work.

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List of Abbreviations

ACEi = Angiotensin-converting enzyme inhibitors

ARB = angiotensin II receptor blockers

ARNI = ARB/neprilysin inhibitor

aHR = Adjusted Hazard Ratio

BB = Beta-blockers

DAPA-HF = Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

DELIVER = Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

DM = Diabetes Mellitus

DPP-4i = Dipeptidyl peptidase IV

EF = Ejection Fraction

EMPA-REG = Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

EMPEROR Preserved = Empagliflozin in Heart Failure with a Preserved Ejection Fraction

EMPEROR Reduced = Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure

GDMT = guideline-directed medical therapy

GLP-1RA = Glucagon like peptide-1 receptor agonist

HR = Hazard Ratio

HFC = Heart Function Clinic

HFmrEF = Heart failure with mid-range ejection fraction

HFpEF = Heart failure with a preserved ejection fraction

HFrEF = Heart failure with a reduced ejection fraction

MRA = Mineralocorticoid receptor antagonists

OR = Odds ratio

SGLT2 inhibitor = Sodium Glucose Transporter 2 inhibitor

T2DM = Type 2 Diabetes Mellitus

Introduction

DM is a well-established risk factor for adverse prognosis in patients with HF. The combination of HF and DM confers an increased risk for hospitalization and worse health outcomes[2]. The prevalence of DM among patients with HF is 24%, over two times higher than the population average.[3] SGLT2 inhibitors have been commercially available for over ten years but, until recently, were primarily used to treat T2DM as a glucose-lowering agent, where there is now evidence for their use in heart failure regardless of the ejection fraction.[4]

SGLT2 inhibitors in Heart Failure

SGLT2 inhibitors reduce blood glucose by inhibiting glucose reabsorption in proximal tubules and by promoting urinary glucose excretion.[5] There are multiple sodium-glucose co-transporters throughout the body, but SGLT2 makes up the majority of glucose reabsorption in the kidneys (90%).[6] Dapagliflozin and Empagliflozin are currently approved for HF in Canada and are both selective inhibitors to SGLT2, with Empagliflozin being the most selective out of all currently available.[7, 8] In 2015, the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG) study demonstrated that HF hospitalizations decreased by 35% following SGLT2 inhibitor treatment.[9] It was then hypothesized that SGLT2 inhibitors had direct effects on cardiac cells. SGLT2 inhibitors are known to have indirect effects on the cardiac system, which should not be understated. Specifically, these have been shown to lower blood glucose, which was their primary intention. Additionally, they have a small but significant impact on weight loss, typically between 1-3 kg lost.[10] They have also been found to have a small but significant drop in blood pressure.[11] Additionally, the renal protective effects are well known and have been

reflected in modern guidelines.[12] These indirect effects are well known and agreed upon as common mechanisms that make SGLT2 inhibitors cardio-protective.

Directly, SGLT2 inhibitors also work by inhibiting sodium-hydrogen exchangers in the myocardium, which increases the concentration of sodium ions in mitochondria, a common electrolyte disturbance in heart failure and something that seems to exert more positive effects during states of stress.[6, 13] The natriuretic effect which was found to be quite substantial in animal models, contributes to improvements in preload and afterload.[14] Recently, SGLT2 inhibitors have been found to suppress apoptosis in different disease states, which can improve myocardial fibrosis by preventing cardiac apoptosis.[15] SGLT2 inhibitors have also been found to enhance macrophage activation, resulting in reduced infiltration of myofibroblasts and collagen accumulation, another mechanism that likely improves and prevents myocardial fibrosis.[16]

In HF ketone body concentrations are increased and thought to be increased in response to stress in HF.[17] SGLT2 inhibitors increase ketone bodies through enhanced gluconeogenesis.[18] Increased ketone bodies are known to decrease adverse cardiac remodeling, oxidative stress and inflammation.[19] Since ketone bodies are a powerful source of energy for HF these increased ketone bodies are thought to have a positive effect on heart failure.[20]

Given these effects, it is not surprising that SGLT2 inhibitors have been proven efficacious in clinical trials. In 2019, the first outcome trial of SGLT2 inhibitors in T2DM patients with HFrEF reported reduced all-cause mortality and CV mortality.[21] Subsequently, the Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction (DAPA-HF) and Cardiovascular and

Renal Outcomes with Empagliflozin in Heart Failure (EMPEROR Reduced) trials demonstrated a reduction in the risk of worsening HF or CV mortality in patients with HF independent of DM status.[22, 23] In 2021, the Empagliflozin in Heart Failure with a Preserved Ejection Fraction (EMPEROR Preserved) trial reported that the risk of CV mortality or HF hospitalization was lower for patients treated with empagliflozin with a left ventricular ejection fraction (LVEF) greater than 40% known as heart failure with mid-range ejection fraction (HFmrEF) and heart failure with a preserved ejection fraction (HFpEF) [24] – a result confirmed by the Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction, (DELIVER) trial with dapagliflozin in 2022.[25] These clinically important improvement in outcomes have also translated to a meaningful improvement in functional status as well.[26]

Diabetes-Specific Considerations in Heart Failure

In addition to SGLT2 inhibitor, there has been an abundance of research surrounding other diabetic medications and cardiac outcomes. The main classes of medications with specific considerations in addition to SGLT2 inhibitors are sulfonylureas, GLP-1RAs and DPP4 inhibitors. Recently, GLP-1RA have been shown to be beneficial compared to DPP4 inhibitors for preventing major adverse CV events. However, sulfonylureas were associated with worse outcomes for major adverse CV events.[27] This has previously been shown not to have an increased risk of death or HF, so potentially this is related more so to ischemic related events rather than HF.[28]

Sulfonylureas have been around for decades and are primarily used to treat type 2 DM. Primarily, their mechanism of action is to close ATP-sensitive K-channels in the pancreatic beta-

cell plasma membrane.[29] Several sulfonylureas have previously been shown to exhibit high-affinity blockage of cardiac mitochondrial ATP-sensitive potassium channels (mitoKATP), and are thought to interfere with ischemic preconditioning, an important mechanism of cardiac protection.[30] Glyburide is a high cardiac mitoKATP high-affinity, and gliclazide is a low-affinity mitoKATP sulfonylurea.[30] Overall, the usage of sulfonylurea is still inconclusive, but likely to not be superior to other treatment options.

GLP-1RAs are a new area of research interest, given their benefit in obesity.[31] In patients with HFpEF they have been shown to significantly improve symptoms and weight loss, which both can be a challenge in HF patients.[32] Data in HFrEF is limited, but early analysis may appear to have a slightly worse outcome for patients with HFrEF.[32] Specifically, in the EXSCEL trial, heart failure hospitalization in the group with an EF of less than 40% had an OR of 1.9 (1.02, 2.83) when being treated with Exenatide.[33] Further research for HFrEF and HFmrEF is warranted for this class.

Gastric inhibitory peptides did not seem to demonstrate benefit in cardiovascular disease or weight loss. However, there is now a dual GLP-1 and gastric inhibitory peptide (GIP) called tirzepatide and early findings are that this may have superior efficacy in terms of glycemic control and weight loss.[34, 35] More evidence is needed for conclusive recommendations in HF and CVD.

DPP-4 inhibitors also have limited evidence in HF. It is thought that the sympathetic activation of certain DPP-4 inhibitors may cause harm in HF.[36] DPP-4 activity is decreased in

heart failure, and it compensates against the elevated sympathetic activity, inhibiting this decreases this adaptive mechanism, theoretically causing myocardial damage.[37] This has been shown in clinical trials, with saxagliptin to cause an increased risk or hospitalization for heart failure.[38] This has not been replicated with other DPP-4 inhibitors. and they are typically deemed safe in HF.[39] It was even shown that there was no inferiority between linagliptin and glimepiride on major adverse CV outcomes.[34]

Objective

Given the efficacy of SGLT2 inhibitors in the HF and DM population from randomized trials, we designed this study to compare the uptake of SGLT2 inhibitors and associated outcomes in two cohorts: a population-based cohort of all adults with DM and HF in Alberta, Canada, and a specialized heart function clinic (HFC) cohort based at the Mazankowski Alberta Heart Institute (MAHI) in Edmonton, Alberta. Additionally, within the HFC cohort, we aim to evaluate outcomes, quality of life (QoL) and GDMT utilization in patients with and without DM.

Methods

Population-Based Cohort and Design

We conducted a population-based retrospective cohort study in the province of Alberta, Canada. The 4.4 million residents of Alberta have universal healthcare, and virtually all are covered by the Alberta Health Care Insurance Plan (AHCIP). Alberta has an integrated healthcare system that allows for the capture and linkage, based on a unique patient healthcare number, of most encounters with the healthcare system. The health administrative data includes the Discharge Abstract Database (DAD) (for all acute care hospitalizations and collects up to 25 International Classification of Diseases, Tenth Revision diagnosis codes, Canada (ICD-10-CA), and up to 20 procedures codes); National Ambulatory Care Reporting System (NACRS) (for all emergency department visits and hospital-based ambulatory care, and collects up to 10 ICD-10-CA diagnosis codes and up to 10 procedure codes); Pharmaceutical Information Network (for community medication dispensations); the provincial laboratory databases; and the provincial registry (to identify death date, residence location). Additionally, the echocardiogram data was acquired from the MAHI and Libin Cardiovascular Institute of Alberta (Calgary) databases (both are tertiary care centres) using each patient's personal health identifier to stratify patients based on LVEF into HFrEF (LVEF <40%), HFmrEF (LVEF 40-49%), and HFpEF (LVEF ≧50%).

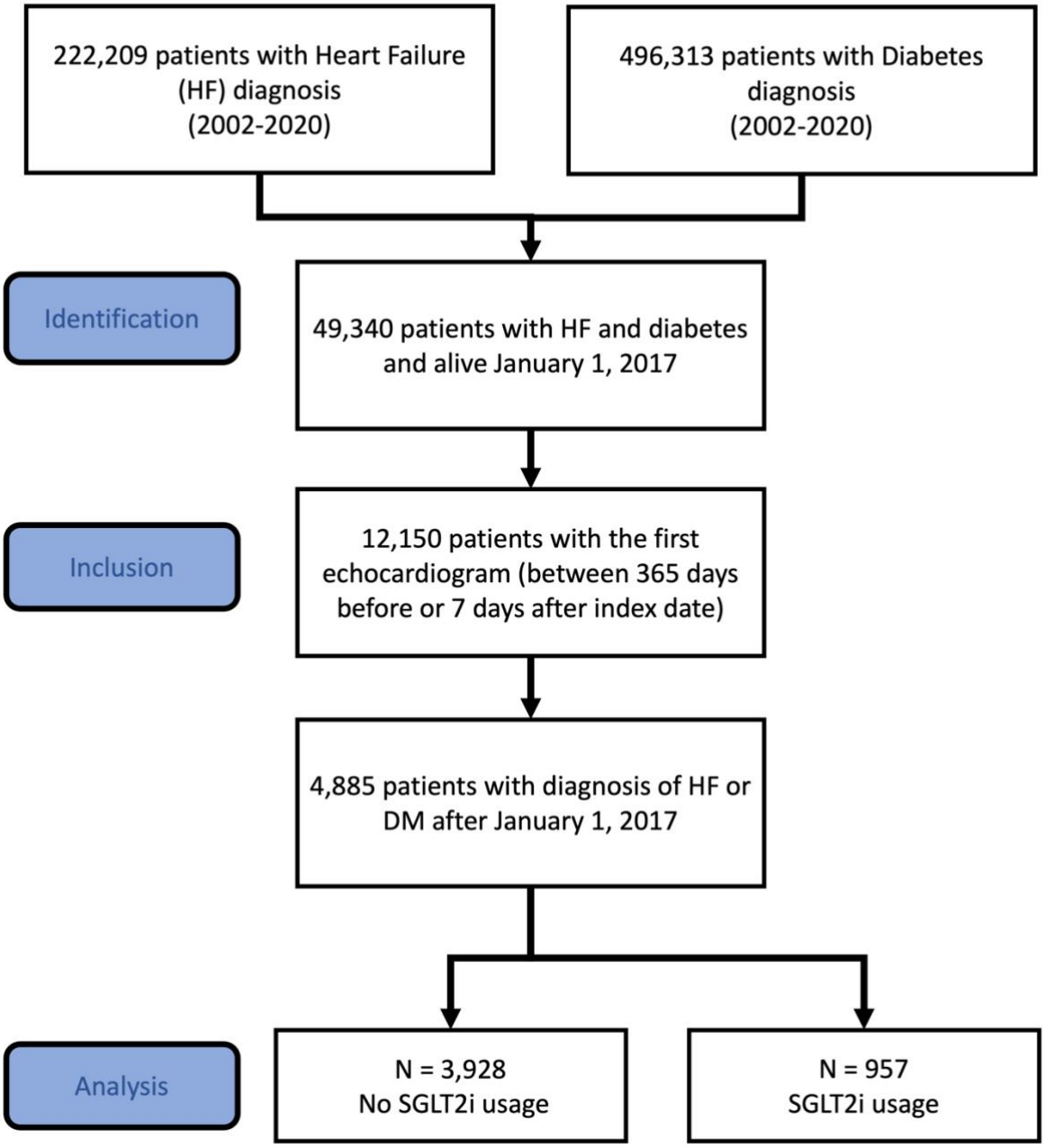
We identified all Alberta residents aged 18 years and above with a diagnosis of T2DM and HF that were alive by the index date, which was defined as the latest of either HF diagnosis, DM diagnosis or January 1, 2017 (**Figure 1**). From this, we identified those individuals with a first echocardiogram between one year prior and seven days after their index date. We classified patients as SGLT2 inhibitor users or not based on dispensation records between their index date

and March 31, 2022, through a time-varying approach. Patients who were using SGLT2 inhibitors at baseline were included in the SGLT2 inhibitor cohort for the duration of follow-up (or until they stopped the medication), whereas patients who started SGLT2 inhibitor after baseline were moved to the SGLT2 inhibitor cohort at the time they initiated treatment.

For further analysis, we created two more cohorts, in addition to the cohort mentioned above (cohort 1). We created an inclusion (cohort 2) and exclusion (cohort 3) cohort based on the RCT eligibility criteria. We excluded those with: 1) prior (1-year look back from index date) median value of B-type natriuretic peptide (BNP) <100 pg/mL or BNP <200 pg/mL with history of atrial fibrillation; or 2) prior (1-year look back from index date) median value of N-terminal pro b-type natriuretic peptide (NT-proBNP) <300 ng/L or NT-proBNP <900 ng/L with a history of atrial fibrillation; or 3) estimated glomerular filtration rate (eGFR) < 25 mL/min/1.73m^2; or 4) documentation of amyloidosis, Fabry disease, Hemochromatosis, hypertrophic obstructive cardiomyopathy (HOCM), constrictive pericarditis, liver disease, heart transplant, or dialysis. This was to ensure a similar population to the major RCTs that studied SGLT2 inhibitor usage in patients with HF.[40]

This part of the study was conducted with approval from the University of Alberta Health Research Ethics Board in accordance with the ethical principles of the Declaration of Helsinki and with waiver of individual patient consent since de-identified data was used (Ethics Approval No. Pro00010852).

Figure 1: Population cohort enrolment flow chart, STROBE diagram



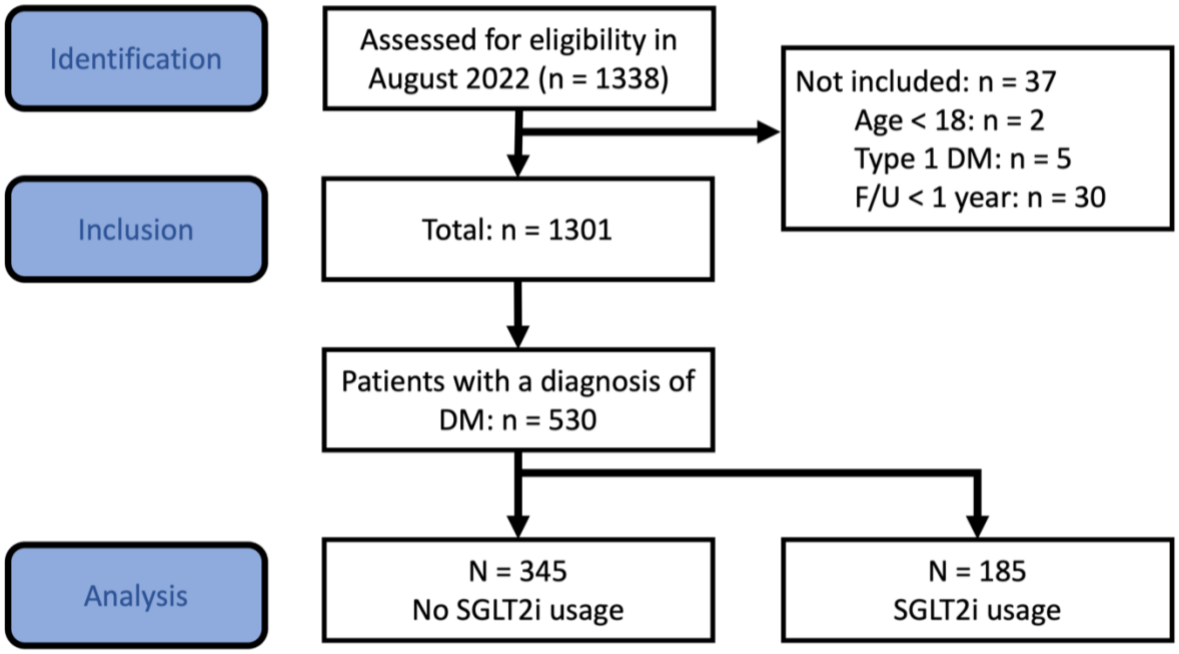
STROBE, Strengthening the Reporting of Observational Studies in Epidemiology. F/U: Follow up time.

Specialized Clinic Cohort Study and Design

Since February 2018, over 1600 patients attending appointments at the MAHI HFC have been enrolled in a prospective registry. This HFC is a tertiary referral centre in Alberta, Canada, for a catchment of over two million adults. The clinic specializes in a multi-disciplinary care approach for managing HF, including nurse practitioners, social workers, dieticians, and pharmacists. Patients enrolled had a diagnosis of HF confirmed by a cardiologist at the HFC. Patients were followed according to the usual standard of care, and prescriptions were at the attending physician's discretion. This part of the study was conducted with approval from the University of Alberta Health Research Ethics Board in accordance with the ethical principles of the Declaration of Helsinki and with individual patients' written informed consent (Pro00077124).

We excluded patients younger than 18 years of age, with type 1 DM, or with less than one year of follow-up time (n = 37) (**Figure 2**). QoL assessments were conducted on enrollment using the shortened Kansas City Cardiomyopathy Questionnaire (KCCQ-12). KCCQ-12 scores were derived from physical limitations, symptom burdens, social limitations and QoL domains and summarized on a scale of 0 to 100. Review of electronic medical records in combination with accessing the linked healthcare administrative databases available through Alberta Health Services was performed for all patients to gather clinical characteristics, comorbidities, medications, laboratory values, and clinical outcomes up until July 31, 2022, as we have described previously.[41]

Figure 2: HFC cohort enrolment flow chart, STROBE diagram



STROBE, Strengthening the Reporting of Observational Studies in Epidemiology. F/U: Follow up time.

Clinical Characteristics

For the population-based cohort, we used DAD and NACRS records from the five years prior to cohort enrollment to define baseline comorbidities (previously shown to have a specificity of greater than 98% for cardiovascular conditions) (**Table 1**).[42] We defined LVEF levels from the echocardiographic database using the echocardiogram result closest to the index date. We collected data on dispensations for beta-blockers (BB), angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB), mineralocorticoid receptor antagonists (MRA), ARB/neprilysin inhibitor (ARNI), Statins, SGLT2 inhibitor, Dipeptidyl peptidase 4 inhibitors (DPP-4-I), sulfonylureas, insulin, glucagon-like peptide-1 agonists (GLP-1) in the six months prior to the index date. The Pampalon Material Deprivation Index was used as a proxy for socioeconomic status.[43]

For the specialized-clinic cohort, demographics, primary HF etiology, echocardiographic parameters, comorbidities, laboratory values, and medications were obtained through electronic chart review. DM status was described as any patient with a hemoglobin A1C greater than 6.5% at enrollment or throughout the study. A time varying SGLT2 inhibitor prescription was used for the date of SGLT2 inhibitor initiation based on the same approach as for the population level cohort stated earlier. CV hospitalizations were obtained through admission diagnosis with ICD-10-CA for all provincial hospitalizations and defined as any hospitalization related to a cardiac cause (HF, acute coronary syndrome, ventricular arrhythmias, sudden cardiac death, stroke, atrial fibrillation, atrial flutter, cardiomyopathy). The primary outcomes were all-cause mortality and death/CV hospitalization.

Table 1: Definitions based on ICD-9 and ICD-10 codes

	ICD-9 Codes	**ICD-10 codes**
Diabetes (1 hit DAD or 2 hits CLM within 2-year period-NDSS))	250.x	E10.x, E11.x, E13.0, E13.1, E14.0, E14.1
Heart failure (1 DAD/1 NACRS/ 2 CLM within 1 year)	428.x	I50.x
Cardiovascular disease (CVD) (1 hit DAD/1 hit NACRS/1 hit CLM) 3 years prior to index date	398.9, 402.0, 402.1, 402.9, 404.0, 404.1, 404.9, 425.4, 425.5, 425.7, 425.8, 425.9, 428, 410, 411, 412, 413, 426, 427, 427.5, 427.9, 798, 362.3, 430, 431, 432, 433, 434, 435, 436, 437, 438, 427.3	I50, I21, I20.0, I47.2, I49.0, I46.1, H34.1, I63, I64, I61, I60, G45, I48
UTI (1 hit DAD/1 hit NACRS/1 hit CLM) from index until end of follow-up (die/ immigrate or March 31, 2022)	599.0	N390, N398, N399
Acidosis (1 hit DAD/1 hit NACRS/1 hit CLM) from index until end of follow-up (die/ immigrate or March 31, 2022)	276.2	E101, E111, E121, E131, E141, E872
Hypertension (1 hit DAD/1 hit NACRS/1 hit CLM) 5 years prior to index date	401-405	I10, I11, I12, I13, I15
Dyslipidemia (1 hit DAD/1 hit NACRS/1 hit CLM) 5 years prior to index date	272	E78
Myocardial infarction (1 hit DAD/1 hit NACRS/1 hit CLM) 5 years prior to index date	410,412	I21, I22, I252

Atrial fibrillation (1 hit DAD/1 hit NACRS/1 hit CLM) 5 years prior to index date	427.3	I48
Cerebrovascular Disease (1 hit DAD/1 hit NACRS/1 hit CLM) 5 years prior to index date	430,431,433,434,435,436, 362.3	H341, I63, I64, I61, I60, G45
COPD (1 hit DAD/1 hit NACRS/1 hit CLM) 5 years prior to index date	491,492,496	J41, J42, J43, J44
Depression (1 hit DAD/1 hit NACRS/1 hit CLM) 5 years prior to index date	296.2,296.3,296.5,300.4,309,311	F204, F313, F314, F315, F32, F33, F34.1, F41.2, F43.2
Anemia (1 hit DAD/1 hit NACRS/1 hit CLM) 5 years prior to index date	280-285	D50-D64
Chronic Kidney Disease (1 hit DAD/1 hit NACRS/1 hit CLM) 5 years prior to index date	583-586, 592, 593.9	N00-N23
Cancer (1 hit DAD/1 hit NACRS/1 hit CLM) 3 years prior to index date		C77-C80, C00-C26, C30-C43, C45-C76, C81-C85, C88, C90-C97
Amyloidosis	277.3	E85
Fabry	-	E75.21
Hemochromatosis	275.0	E83.11
HOCM	425.1	I42.1
Constrictive pericarditis	-	I31.1
Liver disease	456,572	K704, K711, K721, K729, K765, K766, K767, I850,I859,I864,I982
COPD	491,492,496	J41, J42, J43, J44
Heart transplant	-	Z941
Dialysis	-	Z992

ATC codes		
SGLT2 (PIN data) (from index until end of follow-up (die/ immigrate or March 31, 2022))	A10BK01	dapagliflozin
	A10BK02	canagliflozin
	A10BK03	empagliflozin
	A10BD15	metformin and dapagliflozin
	A10BD16	metformin and canagliflozin
	A10BD19	linagliptin and empagliflozin
	A10BD20	metformin and empagliflozin
Heart Failure/Cardiac Medications/Diabetic medications (PIN data) 6 months prior to index date		
	C09A	ACE
	C09C	ARB
	C09DX04	ARNI
	C07	BB
	C03DA01, C03DA04	MRA
	C10AA, C10BA, C10BX	Statin
	A10BA	Biguanide
	A10BB	Sulphonylurea
	A10BH	DPP4i
	A10BJ	GLP1
	A10A	Insulin

Abbreviations: DAD = Discharge Abstract Database; NACRS = National Ambulatory Care Reporting System; CLM = Practitioner Claims; PIN = Pharmaceutical Information Network

Statistical Analysis

The categorical variables were described using frequency and percentage. The continuous variables were described using means with standard deviations or median with interquartile range (IQR) when appropriate. We compared percentages and means with standard deviations (for normally distributed variables) or medians with 25th and 75th percentiles (for non-normally distributed variables) using ANOVA and Kruskal–Wallis tests, respectively. We compared categorical variables using the chi-squared test. For the analysis of primary outcome (all-cause mortality; death or CV hospitalization), SGLT2 inhibitor use was considered as a time-varying co-variate: specifically, the patient's medication status was updated every interval defined as the number of days covered by the medication (based on days supplied) plus a 120-day grace period (to ensure that no prescriptions were missed). Such intervals were updated until the end of follow-up on March 31, 2022, or censored when appropriate to determine the SGLT2 inhibitor status and outcomes.

Multivariable Cox regression models adjusting for all co-variates (including age, Pampalon material deprivation quintile, rural resident, sex, past medical history [dyslipidemia, myocardial infarction, atrial fibrillation, cerebrovascular disease, chronic obstructive pulmonary disease (COPD), depression, anemia, chronic kidney disease (CKD), cancer], LVEF, medications [ACEi, ARB, ARNI, BB, MRA, Statin, Metformin, Sulphonylurea, DPP-4-I, GLP-1, Insulin]) were conducted to investigate the association between SGLT2 inhibitor use and outcomes within the population cohort. We conducted analyses to determine factors affecting discontinuation following each prescription of SGLT2 inhibitor. Factors associated with discontinuation were examined

using logistic regression with generalized estimating equations method to account for repeated prescriptions.

For the specialized clinic cohort, age and sex were included for all adjustments; the remaining variables considered were atrial fibrillation, cancer, COPD, CKD, HF etiology, HF type, usage of beta-blocker, ACEi/ARB/ARNI, MRA, and device therapy including pacemaker (PM), implantable cardioverter-defibrillator and cardiac resynchronization therapy (CRT). An univariable analysis was first conducted, and the variables with a p-value greater than 0.15 were removed. Forward selection was then completed with an entry p-value of 0.1 and a removal p-value of 0.15. The remaining variables were checked for collinearity using a variance inflation factor of less than 10 (all values were less than 1.5). Based on this method, the variables adjusted for CV hospitalization and mortality were age, sex, CKD, hypertension, and HF etiology. The same variables and HF type, usage of ACEi/ARB/ARNI, and COPD were used to compare association between SGLT2 inhibitor utilization with all-cause mortality.

When analyzing SGLT2 inhibitor utilization in patients with HF and DM, cox-regression with time-varying co-variate analysis was used to account for immortal time bias as outlined by Zhou *et al.* where patients taking an SGLT2 inhibitor were included in the SGLT2 inhibitor cohort while taking, and when they weren't taking, they were included in the non-SGLT2 inhibitor cohort (i.e.: stopped medication, or prior to taking the medication) [44]. Patients prescribed SGLT2 inhibitors were presented as a percentage of patients alive in the registry at any given time. All statistical analyses were performed using SPSS version 28 (IBM Corporation) and SAS version 9.4 (SAS Institute, Cary, NC) with statistical significance considered based on two-tailed $p < 0.05$.

Results

Population-Based Cohort

In the population-based cohort, 4,885 patients with DM and HF (median age 72, 38.9% female, 24.2% HFrEF) were eligible for analyses (**Figure 1, Table 2**). SGLT2 inhibitors were dispensed to 957 (19.6%) total patients prior to March 31, 2022, increasing from 1.2% in 2017 to 26.4% by 2022 (of patients eligible for analysis at a given time) (**Figure 3**). Patients prescribed SGLT2 inhibitors were younger, more often male, with lower deprivation and Charlson comorbidity score. Additionally, the group prescribed SGLT2 inhibitors at baseline had lower rates of atrial fibrillation, COPD, depression, CKD, and cancer but higher rates of dyslipidemia and myocardial infarctions. Patients prescribed an SGLT2 inhibitors had a reduced LVEF and were also on higher rates of other HF guideline-directed medical therapy (GDMT) and diabetic medications (**Table 2**). SGLT2 inhibitor use was associated with fewer deaths (aHR 0.51, 95% CI 0.41–0.63) and fewer composite outcome of deaths/CV hospitalizations (aHR 0.65, 95% CI 0.54–0.77) in the population-based cohort over a median follow-up of 39 months (IQR: 21–49 months) in an adjusted multi-variable analysis (**Figure 4,5, Table 3**).

Table 2 Patient baseline characteristics and management in the population-based cohort of patients with DM and HF (n = 4,885)

	Overall (= 4885)		SGLT2 inhibitor user (n = 957)		Non-user (n = 3928)	
Demographics						
Age (years)	72	(63-81)	67	(59-74)	74	(65-82)
Sex (female)	1898	(38.9%)	278	(29.0%)	1620	(41.2%)
Rural residence	671	(13.7%)	157	(16.4%)	514	(13.1%
Pampalon Material Deprivation Quintile						
Quintile 1	626	(15.9%)	745	(15.3%)	119	(12.4%)
Quintile 2	603	(15.4%)	736	(15.1%)	133	(13.9%)
Quintile 3	663	(16.9%)	847	(17.3%)	184	(19.2%)
Quintile 4	712	(18.1%)	904	(18.5%)	192	(20.1%)
Quintile 5	1107	(22.7%)	249	(26.0%)	858	(21.8%)
Unknown	546	(11.2%)	80	(8.4%)	466	(11.9%)
Charlson Comorbidity						
Score Index	4.0	(3.0-6.0)	4.0	(2.0-5.0)	4.0	(3.0-7.0)
Medical History						
Hypertension	4129	(84.5%)	809	(84.5%)	3320	(84.5%)
Dyslipidemia	1233	(25.2%)	278	(29.0%)	955	(24.3%)
MI	1265	(25.9%)	297	(31.0%)	968	(24.6%)
Atrial Fibrillation	1539	(31.5%)	253	(26.4%)	1286	(32.7%)
COPD	684	(14.0%)	94	(9.8%)	590	(15.0%)
CKD	1368	(28.0%)	184	(19.2%)	1184	(30.1%)
Cancer	1974	(40.4%)	267	(27.9%)	1707	(43.5%)
LVEF group						
HFpEF	3066	(62.8%)	513	(53.6%)	2553	(65.0%)
HFmrEF	639	(13.1%)	138	(14.4%)	501	(12.8%)
HFrEF	1180	(24.2%)	306	(32.0%)	874	(22.3%)
Baseline medications						
ACEi/ARB/ARNI	2874	(58.8%)	633	(66.6%)	2241	(57.1%)

Beta-blocker	2469	(50.5%)	522	(54.5%)	1947	(49.6%)
MRA	419	(8.6%)	106	(11.1%)	313	(8.0%)
Insulin	1103	(22.6%)	299	(31.2%)	804	(20.5%)
Metformin	1911	(39.1%)	582	(60.8%)	1329	(33.8%)
Sulfonylurea	603	(12.3%)	222	(23.2%)	381	(9.7%)
GLP-1/DPP IV	330	(6.8%)	133	(13.9%)	227	(5.8%)

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor/neprilysin inhibitor; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DPP IV, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1;HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MI, myocardial infarction, MRA, mineralocorticoid receptor antagonist; SGLT2 inhibitor, sodium-glucose transporter 2 inhibitor.

Figure 3: Initiation of SGLT2 inhibitors in the population cohort

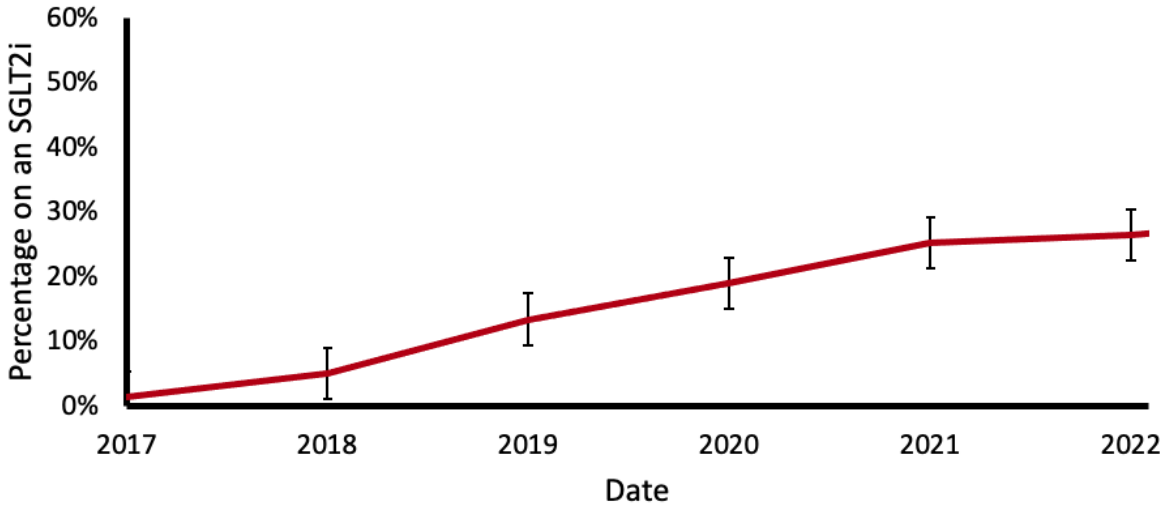


Figure 4: Survival analysis of CV mortality alone for the population cohort comparing patients with diabetes prescribed and not prescribed SGLT2 inhibitor

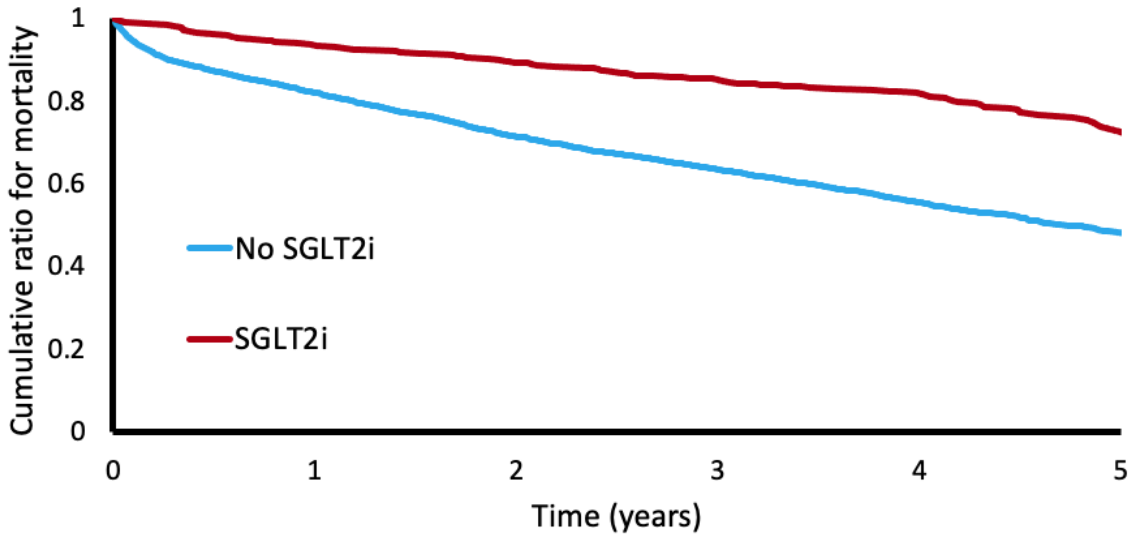


Figure 5: Survival analysis of CV hospitalization or mortality for the population cohort comparing patients with diabetes prescribed and not prescribed SGLT2 inhibitor

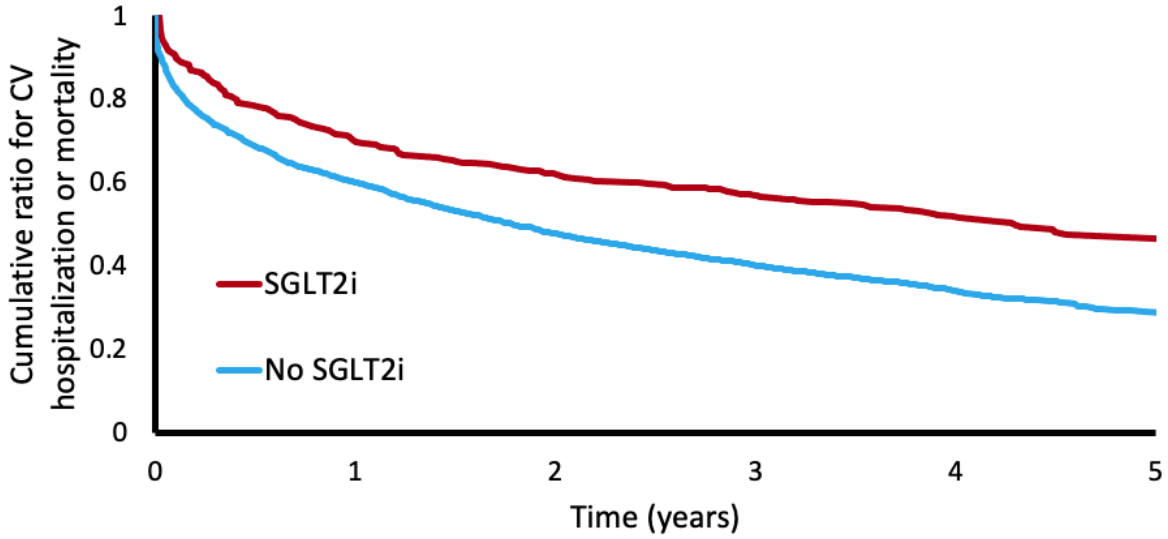


Table 3: Associations between time-varying SGLT2 inhibitor utilization status and outcomes, (n = 4,885)

	Mortality		Composite	
Multi-variable analysis				
	0.51	(0.41-0.63)	0.65	(0.54-0.77)
Demographics				
Sex (female)	0.98	(0.89-1.08)	0.98	(0.91-1.05)
Rural residence	1.00	(0.87-1.14)	1.06	(0.95-1.18)
Charlson Comorbidity				
Score Index	1.68	(1.18-2.39)	1.24	(0.99-1.55)
Medical History				
Hypertension	1.00	(0.87-1.16)	1.15	(1.03-1.30)
Dyslipidemia	0.86	(0.78-0.96)	0.95	(0.88-1.03)
MI	0.93	(0.84-1.04)	1.01	(0.93-1.10)
Atrial Fib	1.12	(1.02-1.23)	1.18	(1.09-1.27)
COPD	1.25	(1.14-1.38)	1.07	(0.99-1.15)
CKD	1.26	(1.14-1.38)	1.13	(1.04-1.21)
Cancer	1.40	(1.25-1.56)	1.08	(0.99-1.19)
LVEF group (referent HFrEF)				
HFpEF	0.92	(0.79-1.06)	0.86	(0.76-0.97)
HFmrEF	0.83	(0.74-0.93)	0.73	(0.67-0.80)

Values are given as n (%) or median (interquartile range). Atrial fib, atrial fibrillation; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MI, myocardial infarction.

When assessing whether these patients would have been included in the landmark trials (cohort 2), 3,138 (64.2%) of the 4,885 patients met the eligibility criteria.[21-25] In the sensitivity analysis restricted to only those patients who would have been eligible for the trials, the associations with lower risk of all-cause mortality (aHR 0.44, 95% CI 0.30–0.58) and death or CV hospitalizations (aHR 0.64, 95% CI 0.52–0.80) were even stronger (**Table 4**). In the analysis restricted to the patients who did not meet trial eligibility criteria based on the criteria above (BNP/NT-proBNP/eGFR too low, or specific comorbidities, n=1,747) with cohort 3, there was still an association with lower risk of all-cause mortality (aHR 0.68, 95% CI 0.48–0.96), but no significant association was seen for the composite outcome (aHR 1.05, 95% CI 0.73–1.51) (**Table 4**).

In the population-based cohort, discontinuation of SGLT2 inhibitors occurred in 33.3% of patients. The only characteristics that were significantly associated with increased risk of discontinuation were rural residence compared to urban residence (33.9% vs 26.7%, $p < 0.001$) and previous history of myocardial infarction compared to no previous history (32.9% vs 26.4%, $p = 0.001$) (**Table 5**).

Table 4: Results in the population-based cohort, by trial eligibility

		All-cause death		Composite	
		HR* (95% CI)	p-value	HR* (95% CI)	p-value
Cohort 1 (n=4,885)	Univariable	0.40 (0.32-0.49)	<.0001	0.63 (0.53-0.74)	<.0001
	Multivariable	0.51 (0.41-0.63)	<.0001	0.65 (0.54-0.77)	<.0001
Cohort 2 (n=3,138)	Univariable	0.36 (0.28-0.47)	<.0001	0.64 (0.52-0.8)	<.0001
	Multivariable	0.44 (0.33-0.58)	<.0001	0.64 (0.52-0.8)	<.0001
Cohort 3 (n= 1,747)	Univariable	0.50 (0.36-0.70)	<.0001	1.13 (0.79-1.62)	0.5151
	Multivariable	0.68 (0.48-0.96)	0.0271	1.05 (0.73-1.51)	0.7954

Comparison of results among the different cohorts. Cohort 1: Population based cohort, Cohort 2: Patients meeting the inclusion criteria of the RCT's, Cohort 3: Patients not meeting the inclusion criteria of the RCT's. RCT = Relevant landmark randomized control trials

Table 5: Patient baseline characteristics based on discontinuation status of SGLT2 inhibitor in the Population-based cohort (n = 957)

	Overall (= 957)		Discontinued (n = 274)		Not Discontinued (n = 683)	
Demographics						
Age (years)	67	(59-74)	67	(56-73)	68	(60-74)
Sex (female)	278	(29.0%)	92	(33.6%)	186	(27.2%)
Rural residence	112	(12.7%)	45	(16.4%)	157	(16.4%)
Pampalon Material Deprivation Quintile						
Quintile 1	119	(12.4%)	32	(11.7%)	87	(12.7%)
Quintile 2	133	(13.9%)	32	(11.7%)	101	(14.8%)
Quintile 3	184	(19.2%)	50	(18.2%)	134	(19.6%)
Quintile 4	192	(20.1%)	61	(23.3%)	131	(19.2%)
Quintile 5	249	(26.0%)	76	(27.7%)	173	(25.3%)
Unknown	80	(8.4%)	23	(8.4%)	57	(8.3%)
Charlson Comorbidity						
Score Index	4	(2-5)	4	(2-5)	4	(2-5)
Medical History						
Hypertension	578	(83.9%)	74	(84.3%)	578	(84.6%)
Dyslipidemia	204	(29.9%)	80	(27.0%)	204	(39.9%)
MI	217	(31.8%)	69	(29.2%)	217	(31.8%)
Atrial Fib	184	(26.9%)	32	(25.2%)	184	(26.9%)
COPD	137	(20.1%)	56	(20.4%)	137	(20.1%)
CKD	186	(27.2%)	81	(29.6%)	186	(27.2%)
Cancer	71	(10.4%)	31	(11.3%)	71	(10.4%)
LVEF group						
HFpEF	513	(53.6%)	161	(58.8%)	352	(51.5%)
HFmrEF	138	(14.4%)	27	(9.9%)	11	(16.3%)
HFrEF	30	(32.0%)	86	(31.4%)	220	(32.2%)

Values are given as n (%) or median (interquartile range). Atrial fib, atrial fibrillation; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; HFmrEF, heart failure with mildly

reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; MI, myocardial infarction.

Specialized Clinic Cohort

In the specialized clinic cohort, we identified 530 patients with diabetes (median age 69, 26.4% female) eligible for analyses: 261 (49.2%) patients had HFrEF, 119 (22.5%) had HFmrEF, and 144 (27.2%) had HFpEF (**Table 6**). The median follow-up was 39 months (IQR: 30–48 months). Of the 530 patients with DM and HF followed in the HFC, 185 (34.9%) patients were prescribed an SGLT2 inhibitor, increasing from 9.8% in 2019 to 49.1 % by March 2022 of patients eligible for analysis (**Figure 6**).

We found no substantial difference in SGLT2 inhibitor usage rate amongst different LVEF subgroups. SGLT2 inhibitor use had no significant difference for all-cause mortality (aHR 0.81, 95% CI 0.54–1.20) and deaths/hospitalizations (aHR 0.88, 95%CI 0.64–1.21) (**Figure 7,8**). There were no clear signals of substantial impacts on the use or dosing of other HF medications within the first year of starting an SGLT2 inhibitor, apart from the finding that 19.4% of patients required a reduction in their diuretic dose (**Table 7**). In the HFC, discontinuation rate of SGLT2 inhibitors was lower than those from the population-based cohort, and only 32 patients (15.4%) permanently discontinued SGLT2 inhibitor, with the most common reason attributed to genitourinary symptoms (primarily yeast infections) seen in nine patients (28.1%) (**Table 8**).

Table 6: Patient baseline characteristics and management of the HFC cohort (n=1,301)

	Overall (n = 1301)		Without DM (n= 771)		With DM (n= 530)	
Demographics						
Age (years)	66	(57-76)	65	(54-76)	69	(60-76)
Sex (male)	911	(70.0 %)	519	(67.3 %)	390	(73.6 %)
Ethnicity						
White	1104	(84.9 %)	675	(87.5 %)	429	(80.9 %)
Indigenous	28	(2.2 %)	12	(1.6 %)	16	(3.0 %)
Latin America	17	(1.3 %)	11	(1.4 %)	6	(1.1 %)
Black	17	(1.3 %)	10	(1.3 %)	7	(1.3 %)
Middle Eastern	21	(1.6 %)	12	(1.6 %)	9	(1.7 %)
Asian	75	(5.8 %)	33	(4.3 %)	42	(7.9 %)
Unknown	39	(3.0 %)	18	(2.3 %)	21	(4.0 %)
Etiology						
IHD	427	(32.8 %)	206	(26.7 %)	221	(41.7 %)
Non-IHD	874	(67.2 %)	565	(73.3 %)	309	(58.3 %)
Medical History						
Hypertension	714	(54.7 %)	338	(43.8 %)	374	(70.6 %)
Atrial Fibrillation	456	(35.0 %)	260	(33.7 %)	196	(37.0 %)
CKD	439	(33.7 %)	202	(26.1 %)	237	(44.7 %)
Cancer	385	(29.6 %)	208	(27.0 %)	177	(33.4 %)
COPD	287	(22.1 %)	150	(19.5 %)	137	(25.8 %)
DLP	304	(23.4 %)	130	(16.9 %)	174	(32.8 %)
Devices						
PM	165	(12.6 %)	94	(12.2 %)	70	(13.2 %)
ICD	278	(21.4 %)	142	(18.4 %)	136	(25.7 %)
CRT	63	(4.8 %)	33	(4.3 %)	29	(5.7 %)
Baseline Medications						
ACEi/ARB/ARNI	1144	(87.9 %)	674	(87.4 %)	470	(88.7 %)
Beta-blocker	1165	(89.5 %)	677	(87.8 %)	488	(92.1 %)

MRA	830	(63.8 %)	471	(61.1 %)	359	(67.7 %)
Insulin	168	(12.9 %)	0	(0.0 %)	168	(31.7 %)
Metformin	278	(21.4 %)	2	(0.3 %)	274	(51.7 %)
SGLT2 inhibitor	92	(7.1 %)	1	(0.1 %)	91	(17.2 %)
Sulfonylurea	93	(7.1 %)	0	(0.0 %)	93	(17.5 %)
GLP-1/DPP IV	34	(2.6 %)	2	(0.3 %)	32	(6.0 %)
Laboratory markers						
BNP (ng/L)	440	(172-976)	401	(157-898)	502	(198-1078)
HbA1c (%)	6.3	(5.8-7.3)	5.8	(5.5-6.1)	7.1	(6.5-8.2)
Creatinine (umol/L)	102	(83-130)	96	(80-119)	114	(89-146)
ACR (mg/mmol)	2.96	(0.8-15.4)	1.59	(0.45-8.20)	3.96	(0.97-16.46)
Hemoglobin (g/L)	133	(119-146)	136	(122-148)	129	(115-129)
Cholesterol (mmol/L)	3.65	(3.09-4.61)	3.94	(3.27-4.83)	3.40	(2.94-4.23)
CKD-Epi (mL/min/1.73m^2)	61	(43-80)	65	(48-82)	52	(37-72)
Echocardiogram						
EF (%)	40.7	(30.4-52.5)	41.1	(31.1-52.5)	40.3	(30.0-52.5)
HFrEF (≤40%)	626	(48.1 %)	365	(47.3 %)	261	(49.2 %)
HFmrEF	262	(20.1 %)	143	(18.5 %)	119	(22.5 %)
HFpEF (≥50%)	389	(29.9 %)	245	(31.8 %)	144	(27.2 %)

Values are given as n (%) or median (interquartile range). P-value column is comparing the cohort with Diabetes vs without Diabetes. A1C, glycated hemoglobin; ACEi, angiotensin-converting enzyme inhibitors; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor/neprilysin inhibitor; BNP, brain natriuretic peptide; CKD, chronic kidney disease; CKD-Epi, equation used to calculate glomerular filtration rate; COPD, chronic obstructive pulmonary disease; CRT, cardiac re-synchronization therapy; DLP, dyslipidemia; DPP IV, dipeptidyl peptidase 4; EF, ejection fraction; GLP-1, glucagon-like peptide 1; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced

ejection fraction; ICD, implantable cardioverter defibrillator; IHD, ischemic heart disease; MRA, mineralocorticoid receptor antagonist; PM, pacemaker; SGLT2 inhibitor, sodium-glucose transporter 2 inhibitor.

Figure 6: Initiation of SGLT2 inhibitors in the population cohort

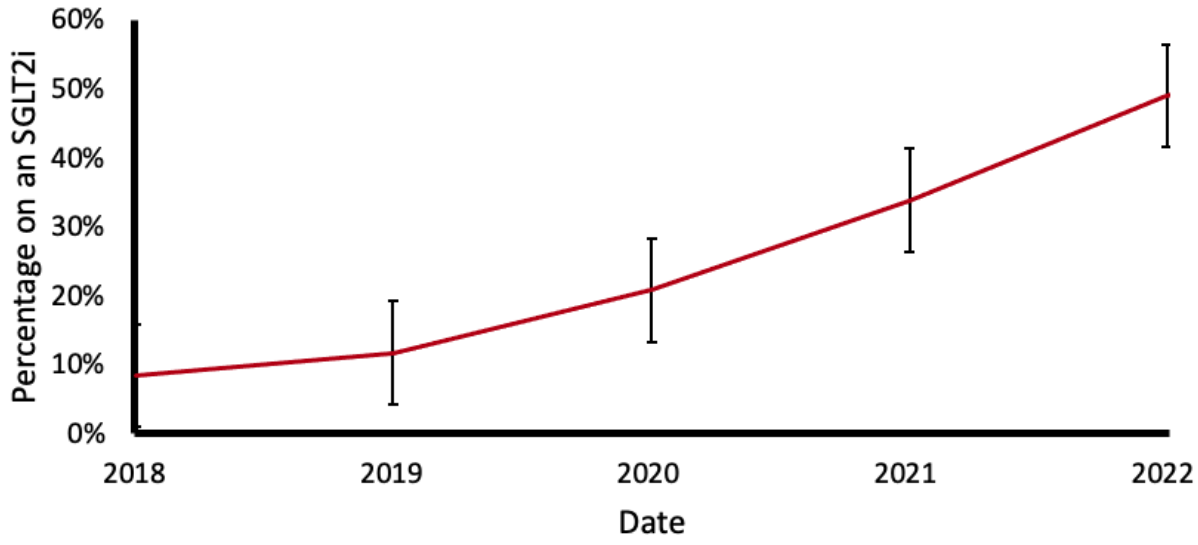


Figure 7: Survival analysis of all-cause mortality alone for the HFC cohort, comparing patients with diabetes prescribed and not-prescribed SGLT2 inhibitor

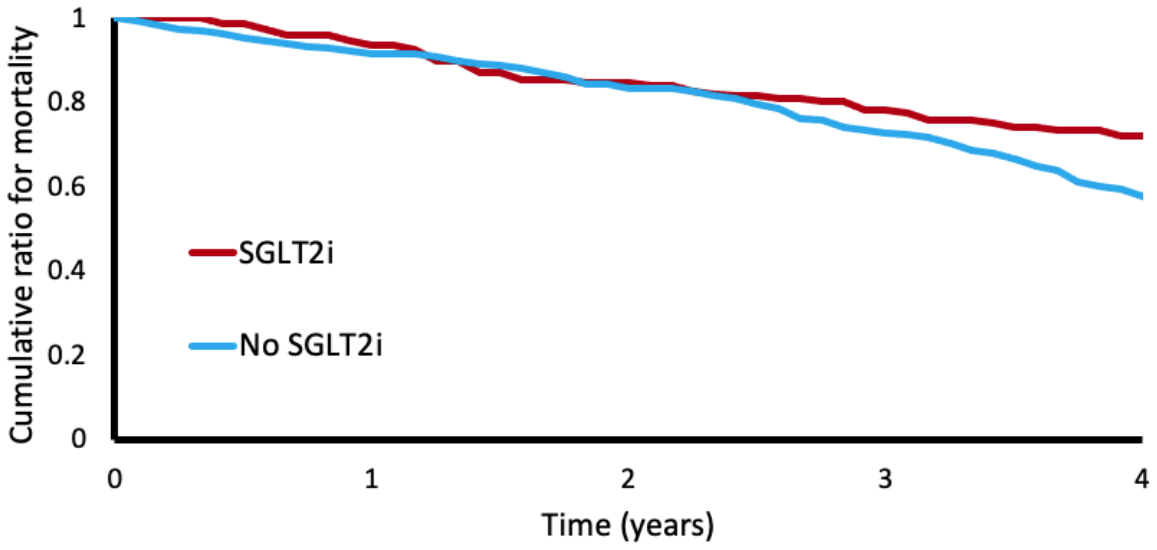


Figure 8: Survival analysis of CV hospitalization and mortality for the HFC cohort, comparing patients with diabetes-prescribed and not prescribed SGLT2 inhibitors

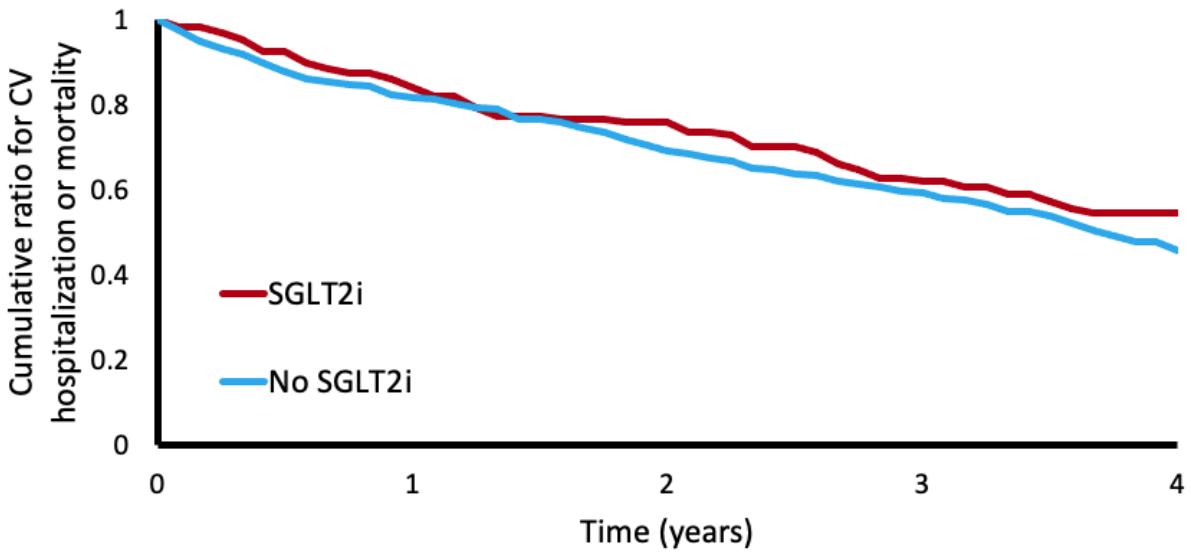


Table 7: Analysis of change in medications after initiating an SGLT2 inhibitor.

	DM medications	Diuretics	ACEi/ARB/ARNI	MRA	Beta-blocker
Increase	8 (4.2%)	12 (6.3%)	20 (10.5%)	7 (3.7%)	8 (4.2%)
Decrease	12 (6.3%)	37 (19.4%)	25 (13.1%)	21 (11.0%)	16 (8.4%)
No change	171 (89.5%)	142 (74.3%)	152 (79.6%)	163 (85.3%)	167 (87.4%)

Follow-up data for n = 208, medication analysis over 12 months after starting an SGLT2 inhibitor in the HFC cohort. ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor/neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist.

Table 8: Analysis of reasons for discontinuation in patients who discontinued SGLT2 inhibitors in the HFC cohort (n = 32)

Rationale for discontinuation	Number (%)
Genitourinary symptoms	9 (28.1%)
DKA	6 (18.8%)
Hypotension	2 (6.3%)
Weight Loss	2 (6.3%)
Other	13 (40.6%)

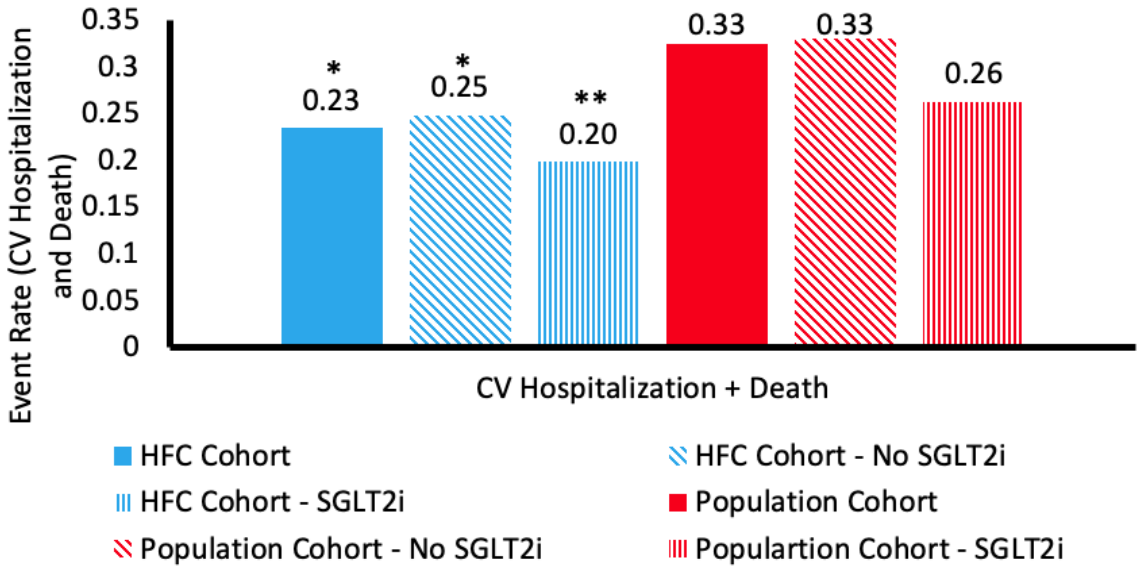
DKA, Diabetic Ketoacidosis

When comparing the event rate per year of CV hospitalization and death, SGLT2 inhibitor non-users experienced 0.248 events per year and SGLT2 inhibitor users experienced 0.198 events per year (rate difference of 0.050, 95% CI -0.003 – 0.103) (**Figure 9**). In comparison, the population cohort saw 0.330 events per year amongst SGLT2 inhibitor non-users and 0.263 events per year in SGLT2 inhibitor users (rate difference of 0.066, 95% CI 0.041 – 0.091). Of note, the utilization of other HF medications in the specialized HFC cohort is much greater than in the population cohort (**Figure 10**).

In total, 17% (n = 90) patients were on a sulfonylurea, only 5 were on glyburide, and none of them had a decrease in EF. Additionally, there was no significant differences in outcomes for patients comparing the different types of SGLT2 inhibitors (empagliflozin vs canagaflozin vs dapagliflozin).

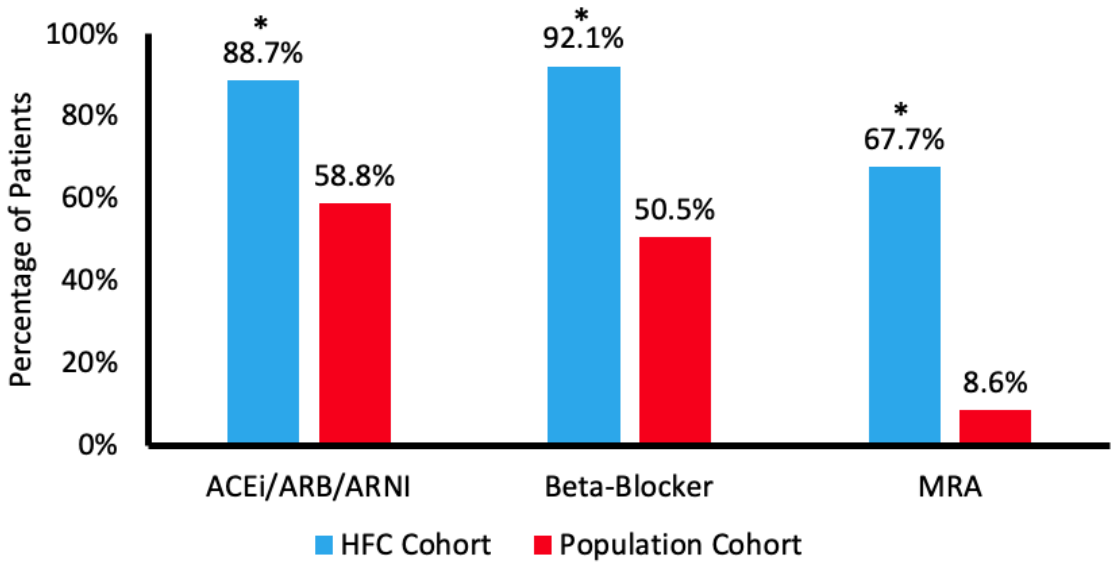
When analyzing the difference amongst the subgroups based on LVEF, there was no difference for HFrEF (p = 0.212, log rank) (**Figure 11**) and HFmrEF (p = 0.577, log rank) (**Figure 12**) at 4 years, whereas there was a difference for HFpEF (p = 0.048, log rank) (**Figure 13**).

Figure 9: Outcomes and characteristics comparing the HFC to the population cohort



* Indicates a p value of <0.001 when comparing HFC cohort to the population cohort, ** indicates a p value of 0.01 when comparing HFC cohort to the population cohort.

Figure 10: Baseline heart failure medications in the population and HFC cohort



* Indicates a p value of <0.001 when comparing HFC cohort to the population cohort

Figure 11: Survival analysis of all-cause mortality for the HFC cohort, comparing patients with diabetes and HFrEF prescribed and not prescribed an SGLT2 inhibitor

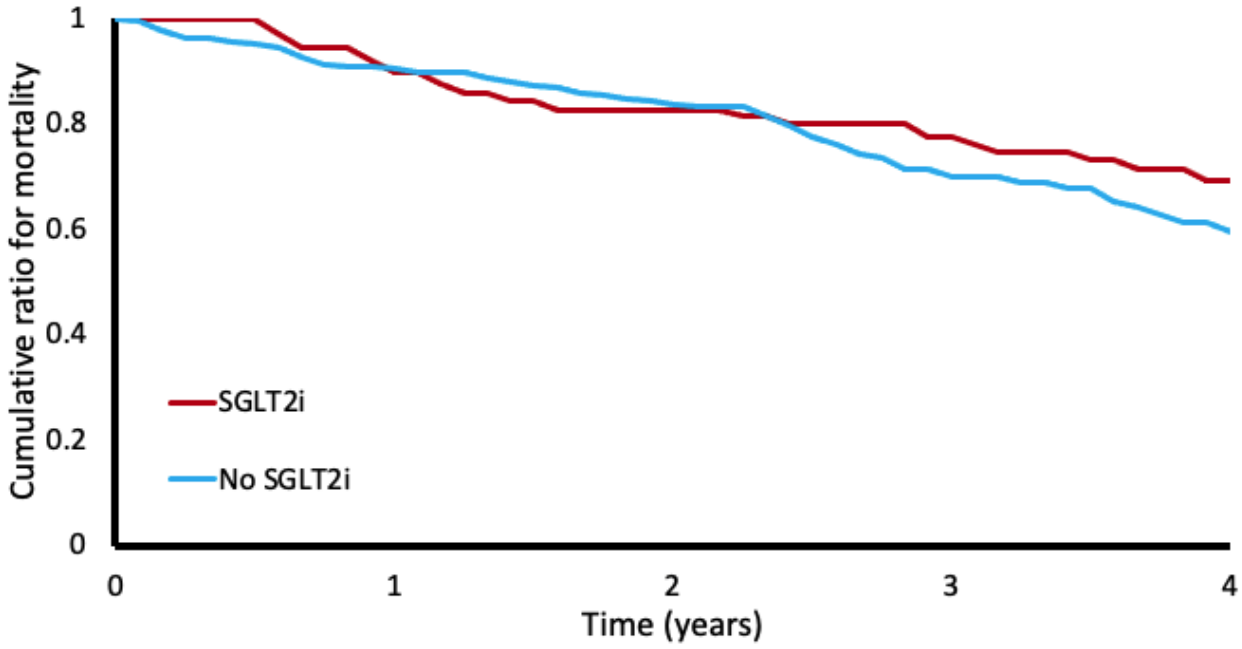


Figure 12: Survival analysis of all-cause mortality for the HFC cohort, comparing patients with diabetes and HFmrEF prescribed and not prescribed an SGLT2 inhibitor

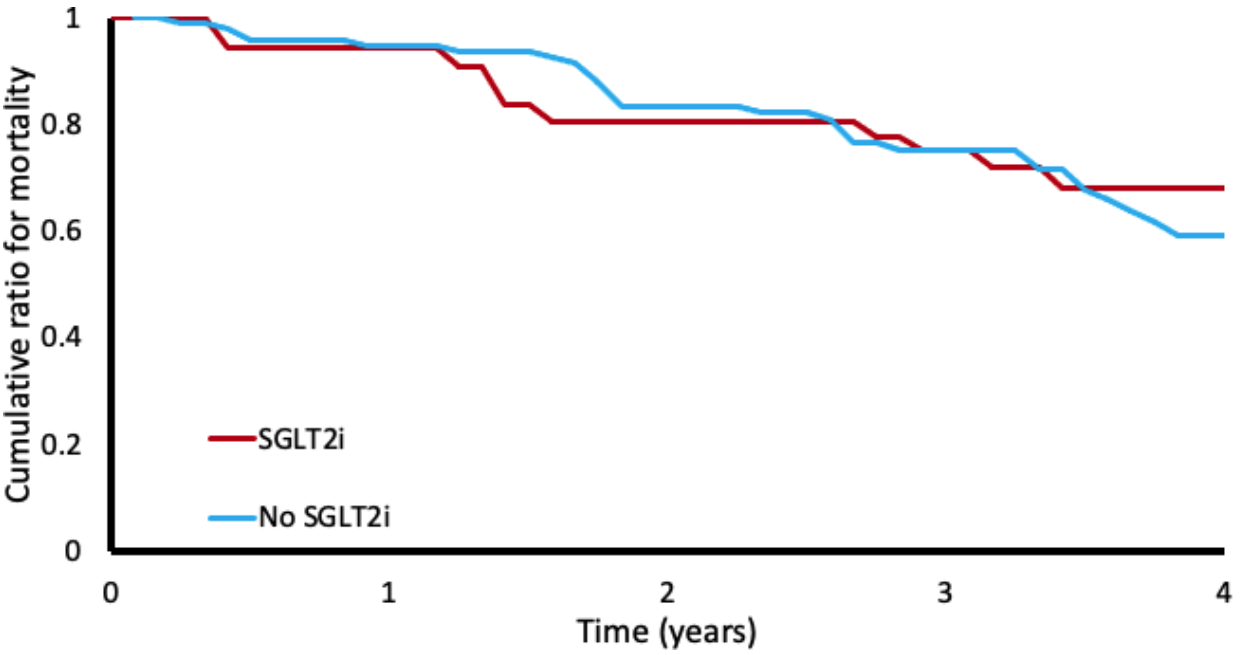
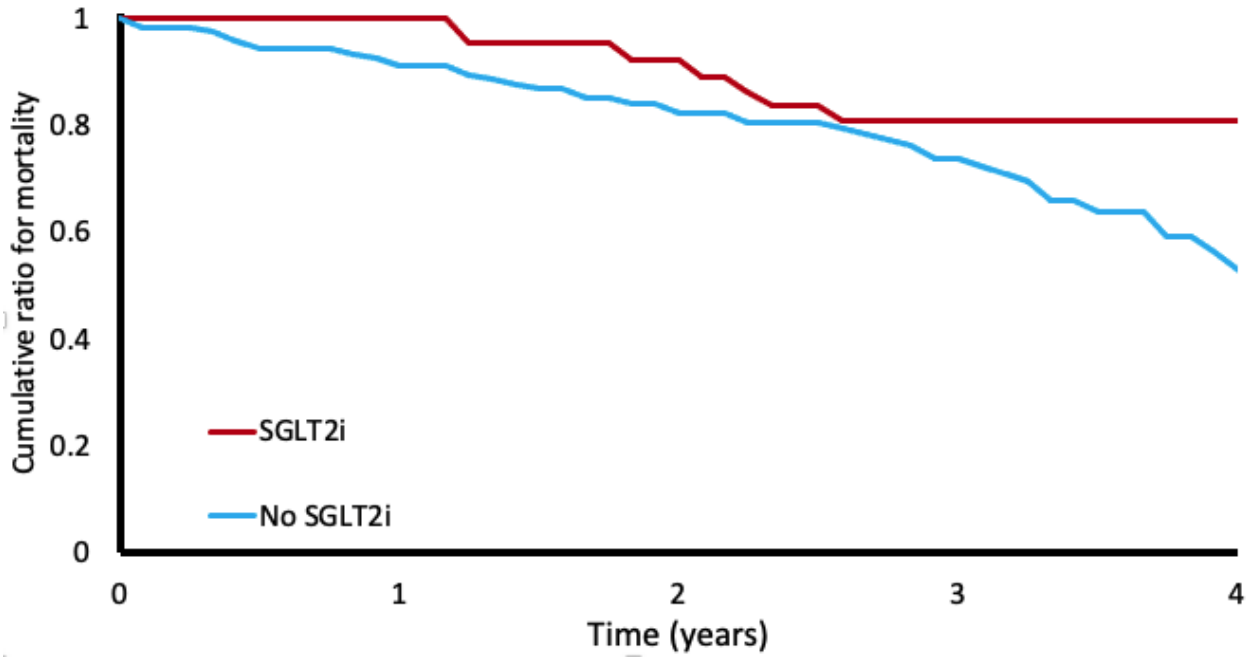


Figure 13: Survival analysis of all-cause mortality for the HFC cohort, comparing patients with diabetes and HFpEF prescribed and not prescribed an SGLT2 inhibitor



When considering the entirety of the specialized clinic cohort (with and without Diabetes) the majority of patients were male (70.0%) and white (84.9%). Overall, 48.1% of patients had HF with reduced EF (HFrEF), 20.1% had HF with mildly reduced EF (HFmrEF), and 29.9% had HF with preserved EF (HFpEF) (**Table 9**). The median follow-up was 38.7 months (IQR: 30.7 – 48.2 months). Patients without DM were more likely to have HFpEF compared to those with DM ($p < 0.05$, **Figure 14**). Patients with DM had higher rates of co-morbidities with the largest differences seen in hypertension (70.6% vs 43.8%), dyslipidemia (32.8% vs 16.9%) and chronic kidney disease (44.7% vs 26.1%), compared to those without DM (all p values < 0.001, **Table 9**). Additionally, it was more common for patients with DM to have HF secondary to ischemic heart disease (IHD) ($p < 0.001$, **Table 9**), however, there is still a large percentage of patients (58.3%, **Table 9)** without IHD, highlighting that HF is not only from ischemia in this patient population.[45]

The main significant difference in GDMT utilization was SGLT2 inhibitor usage across all HF sub-types, which was much higher in the DM group (33.8% vs. 3.1%, $p < 0.001$). Additionally, patients with DM had higher utilization of beta-blockers in the HFmrEF and HFpEF group and higher utilization of mineralocorticoid receptor antagonists in the HFpEF group (all $p < 0.001$, **Figure 15)**. In the HFrEF group for the overall cohort, GDMT utilization was 17.9% for SGLT2 inhibitor, 96.5% for beta-blocker, 82.0% for MRA, and 94.6% for ACEi/ARB/ARNI. Additionally, In the HFrEF group for the overall cohort, 81.0% were on triple therapy and 16.0% on quadruple therapy. There was no difference amongst triple therapy when comparing DM vs non-DM (82.0% vs 79.7%, $p = 0.24$), but due to the differences of SGLT2 inhibitor usage, there was a larger percent of quadruple therapy for the DM cohort (32.2% vs 4.4%, $p < 0.001$). When analyzing patients eligible by July 2021 in the DM cohort, SGLT2 inhibitor usage was up to 51.4%.

Table 9: Baseline characteristics and management of the HFC cohort patients with DM and HF (n = 530)

	Overall (n= 530)		SGLT2 inhibitor users (n= 185)		Non-users (n= 345)	
Demographics						
Age (years)	69	(60-76)	67	(59-72)	70	(60-78)
Sex (female)	140	(26.4%)	36	(19.5%)	102	(29.6%)
Ethnicity						
White	429	(80.9 %)	141	(76.2%)	288	(83.5%)
Indigenous	16	(3.0 %)	7	(3.8%)	9	(2.6%)
Latin America	6	(1.1 %)	0	(0.0%)	6	(1.7%)
Black	7	(1.3 %)	4	(2.2%)	3	(0.9%)
Middle Eastern	9	(1.7 %)	5	(2.7%)	4	(1.2%)
Asian	42	(7.9 %)	19	(10.3%)	23	(6.7%)
Unknown	21	(4.0 %)	9	(4.9%)	12	(3.5%)
Etiology						
IHD	221	(41.7 %)	87	(47.0%)	134	(38.8%)
Non-IHD	309	(58.3 %)	98	(53.0%)	211	(61.2%)
Medical History						
Hypertension	374	(70.6 %)	124	(67.0%)	250	(72.5%)
Atrial Fibrillation	196	(37.0 %)	55	(29.7%)	141	(40.9%)
CKD	237	(44.7 %)	67	(36.2%)	170	(49.2%)
Cancer	177	(33.4 %)	51	(27.6%)	126	(36.5%)
COPD	137	(25.8 %)	33	(17.8%)	104	(30.1%)
DLP	174	(32.8 %)	59	(31.9%)	115	(33.3%)
Devices						
PM	70	(13.2 %)	20	(10.8%)	50	(14.5%)
ICD	136	(25.7 %)	53	(28.6%)	83	(24.1%)
CRT-D	29	(5.7 %)	7	(3.8%)	23	(6.7%)
Baseline Medications						
ACEi/ARB/ARNI	470	(88.7 %)	175	(94.6%)	295	(85.5%)
Beta-blocker	488	(92.1 %)	177	(95.7%)	311	(90.1%)

MRA	359	(67.7 %)	135	(73.0%)	224	(64.9%)
Insulin	168	(31.7 %)	74	(40.0%)	94	(27.2%)
Metformin	274	(51.7 %)	122	(65.9%)	152	(44.1%)
Sulfonylurea	93	(17.5 %)	52	(28.1%)	41	(11.9%)
GLP-1/DPP IV	32	(6.0 %)	24	(13.0%)	8	(2.3%)
Laboratory markers						
BNP (ng/L)	502	(198-1078)	488	(157-965)	510	(212-1196)
HbA1C (%)	7.10	(6.50-8.20)	7.87	(6.85-8.83)	6.90	(6.40-77.70)
Creatinine (umol/L)	114	(89-146)	108	(88-131)	119	(90-163)
ACR (mg/mmol)	3.96	(0.97-16.46)	3.11	(0.85-15.95)	4.57	(1.09-16.76)
Hemoglobin (g/L)	129	(115-129)	134	(123-148)	127	(111-141)
Cholesterol (mmol/L)	3.40	(2.94-4.23)	3.42	(2.82-4.12)	3.39	(2.94-4.25)
CKD-Epi (mL/min/1.73m^2)	52	(37-72)	57	(46-77)	49	(32-71)
Echocardiogram						
HFrEF (≤40%)	261	(49.2 %)	96	(51.9%)	165	(47.8%)
HFmrEF	119	(22.5 %)	43	(23.3%)	76	(22.0%)
HFpEF (≥50%)	144	(27.2 %)	43	(23.2%)	101	(29.3%)

A1C, glycated hemoglobin; ACEi, angiotensin-converting enzyme inhibitors; ACR, albumin-to-creatinine ratio; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor/neprilysin inhibitor; BNP, brain natriuretic peptide; CKD, chronic kidney disease; CKD-Epi, equation used to calculate glomerular filtration rate; COPD, chronic obstructive pulmonary disease; CRT, cardiac re-synchronization therapy; DLP, dyslipidemia; DPP IV, dipeptidyl peptidase 4; GLP-1, glucagon-like peptide 1; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; IHD, ischemic heart disease; MRA, mineralocorticoid receptor antagonist; PM, pacemaker; SGLT2 inhibitor, sodium-glucose transporter 2 inhibitor.

Figure 14: Distribution of EF based on diabetes status in the HFC cohort

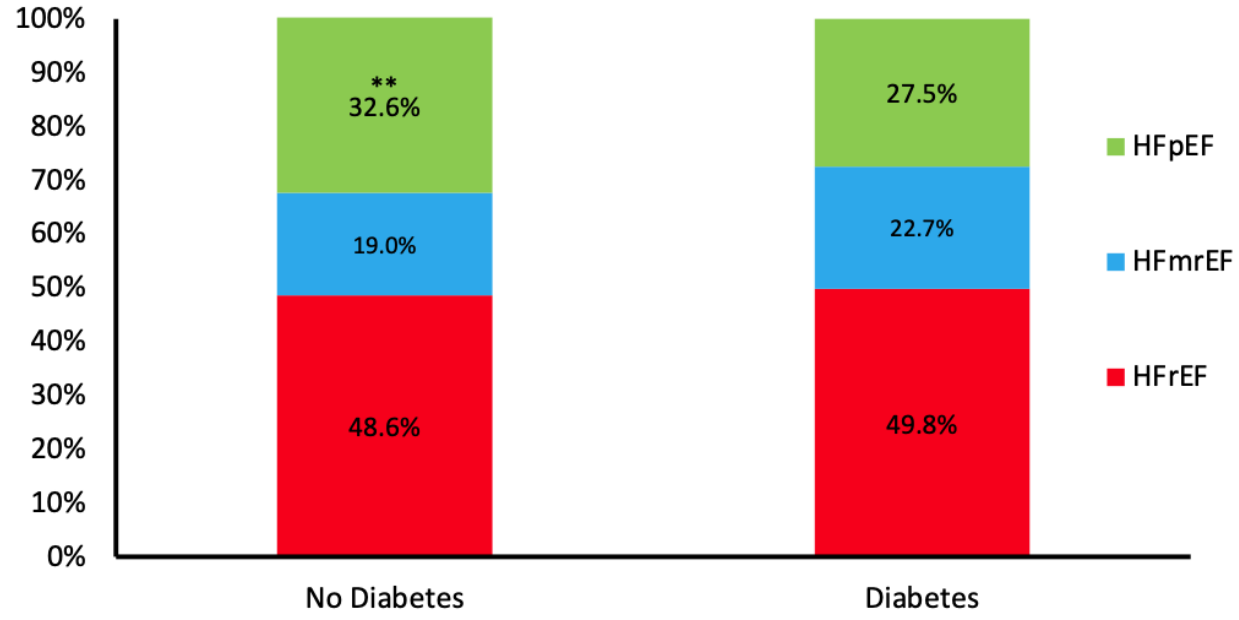
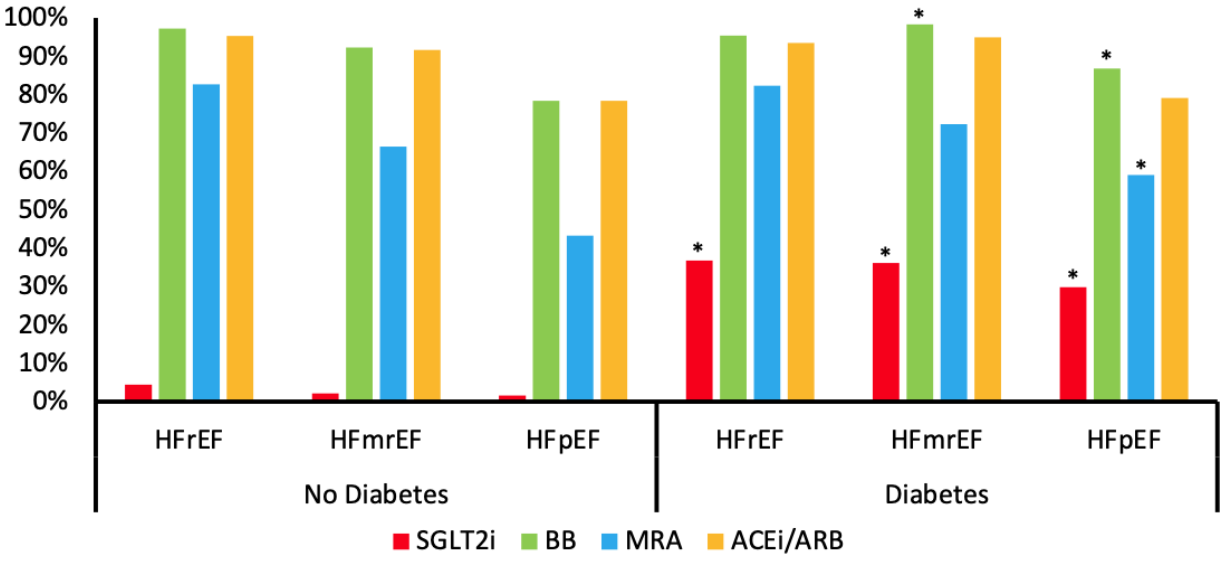


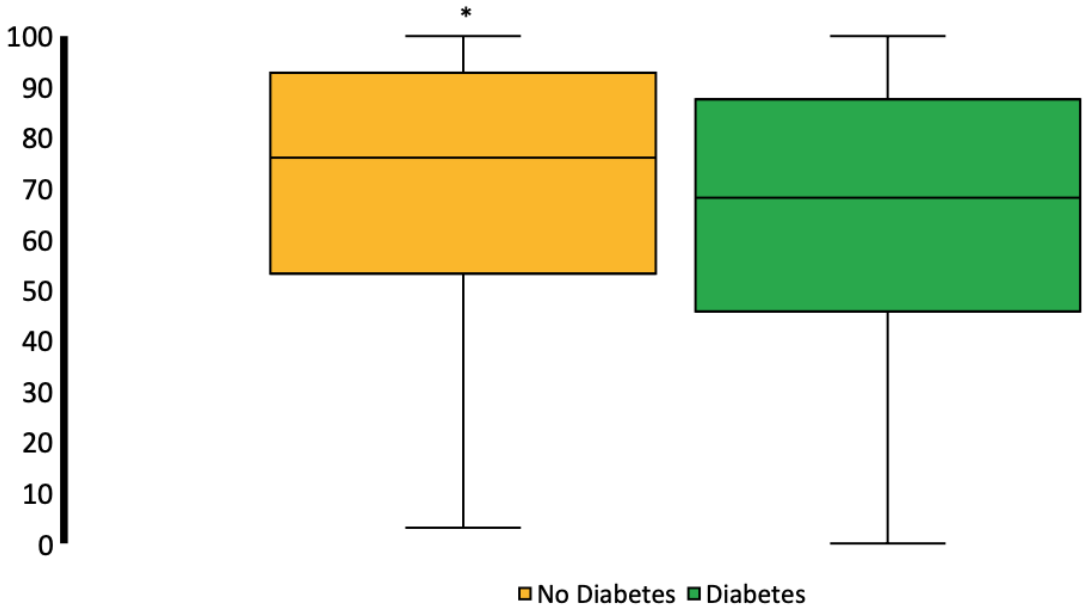
Figure 15: GDMT utilization based on diabetes status and ejection fraction in the HFC cohort



* = p value < 0.001

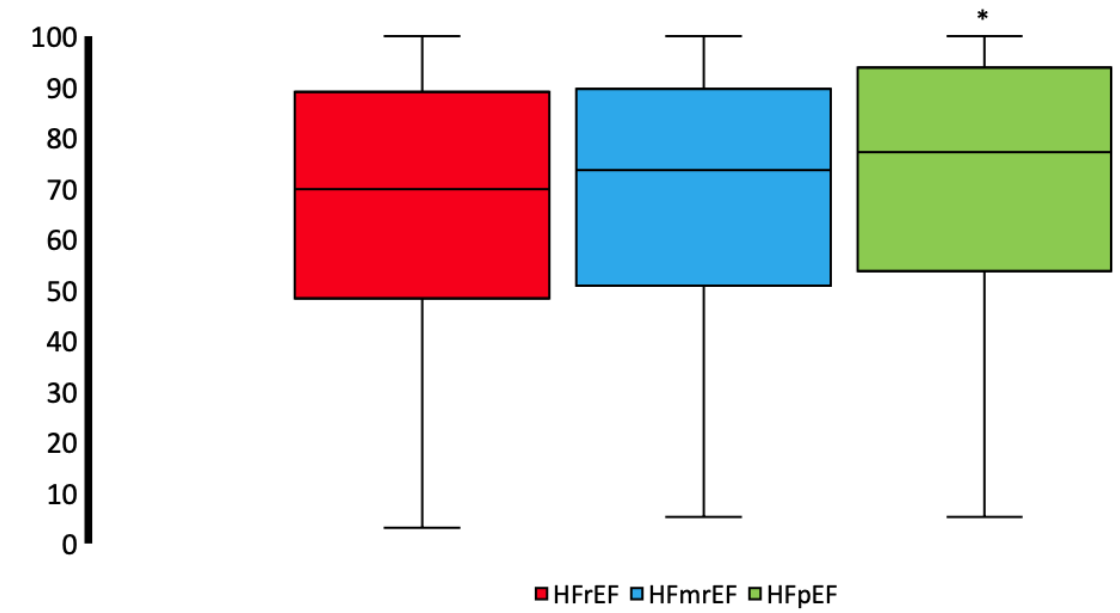
Patient-reported QoL was worse in those with DM (median 68.1, IQR: 45.8 – 87.5) compared to those without DM (76.0, IQR: 53.1 – 92.7, $p < 0.001$) (**Figure 16**). QoL was significantly better in the HFpEF group compared to HFrEF and HFmrEF patients ($p < 0.001$) (**Figure 17**). During a median follow-up time of 38.7 months (IQR: 30.7 – 48.2 months), patients with DM exhibited an increased risk of composite outcomes (aHR: 1.34, 95% CI 1.13 – 1.60) and all-cause mortality alone (aHR: 1.12, 95% CI 1.01 – 1.43) compared to non-DM patients (**Figure 18,19**).

Figure 16: KCCQ-12 scored based on DM status in the HFC cohort



* = p value < 0.001

Figure 17: KCCQ-12 score based on EF in the HFC cohort



* = p value < 0.001

Figure 18: Survival analysis of all-cause mortality for the HFC cohort, comparing DM status

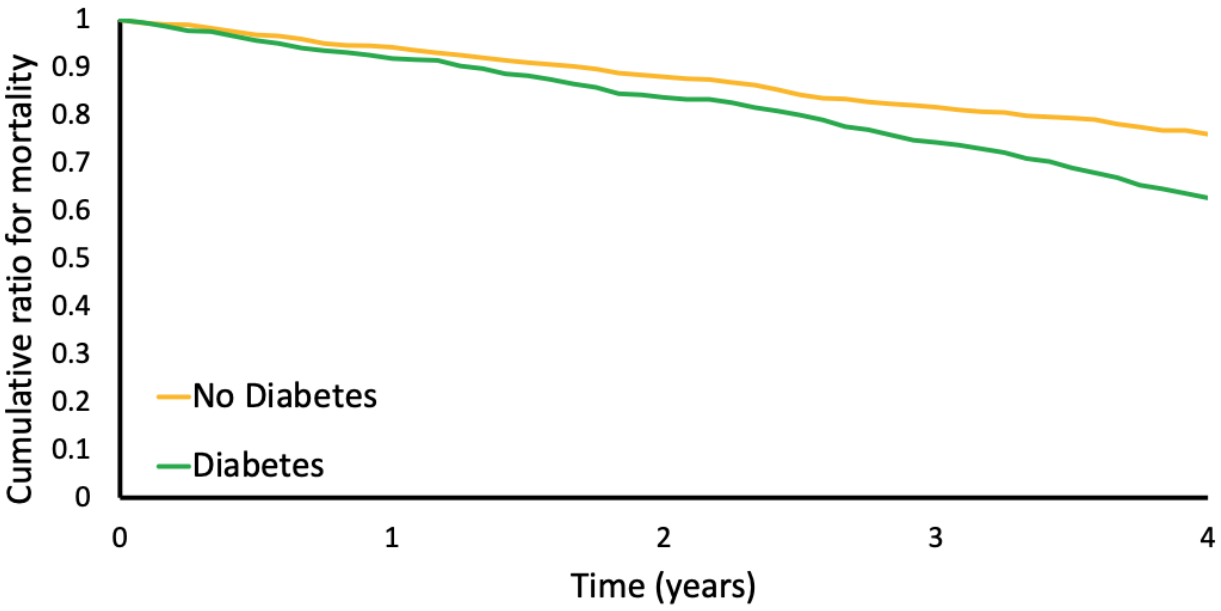
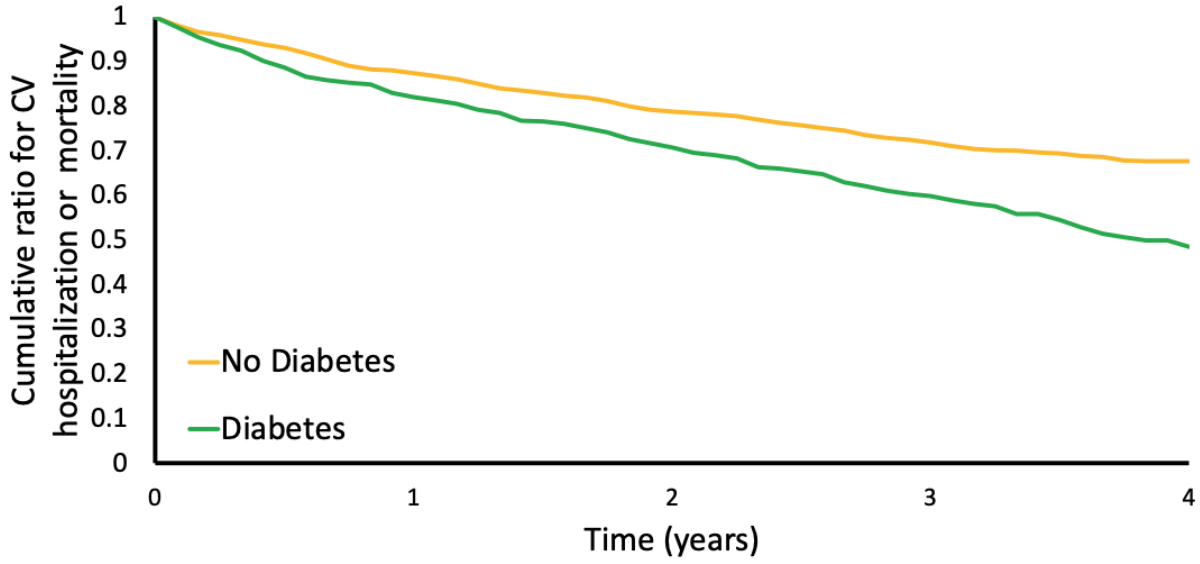


Figure 19: Survival analysis of CV hospitalization and mortality, for the HFC cohort, comparing DM status



Discussion

In patients with DM, HF is up to 4-fold more common than in the general population, and the frequency of concomitant HF and DM is expected to continue to increase as the prevalence of DM increases.[46] As such timely initiation and up-titration of HF medications are essential to improve survival and quality of life in HF patients, especially with SGLT2 inhibitor initiation being reflected in updated guidelines.[47] Moreover, the high prevalence of co-morbidities with DM emphasize the importance of managing other risk factors with disease modifying therapy such as statins, antiplatelets, and antihypertensives. The HFC specializes in a multi-disciplinary care approach for managing HF, including nurse practitioners, social workers, dieticians, and pharmacists (**Figure 20**). Overall, SGLT2 inhibitor up-titration was limited, but higher in the HFC when compared to the population level, SGLT2 inhibitor utilization has a reduced aHR for all-cause death at the population level, and within the HFC cohort, DM has an increased aHR for both all-cause death and CV hospitalizations and all-cause death (**Figure 21**).

Figure 20: Multi-disciplinary HFC

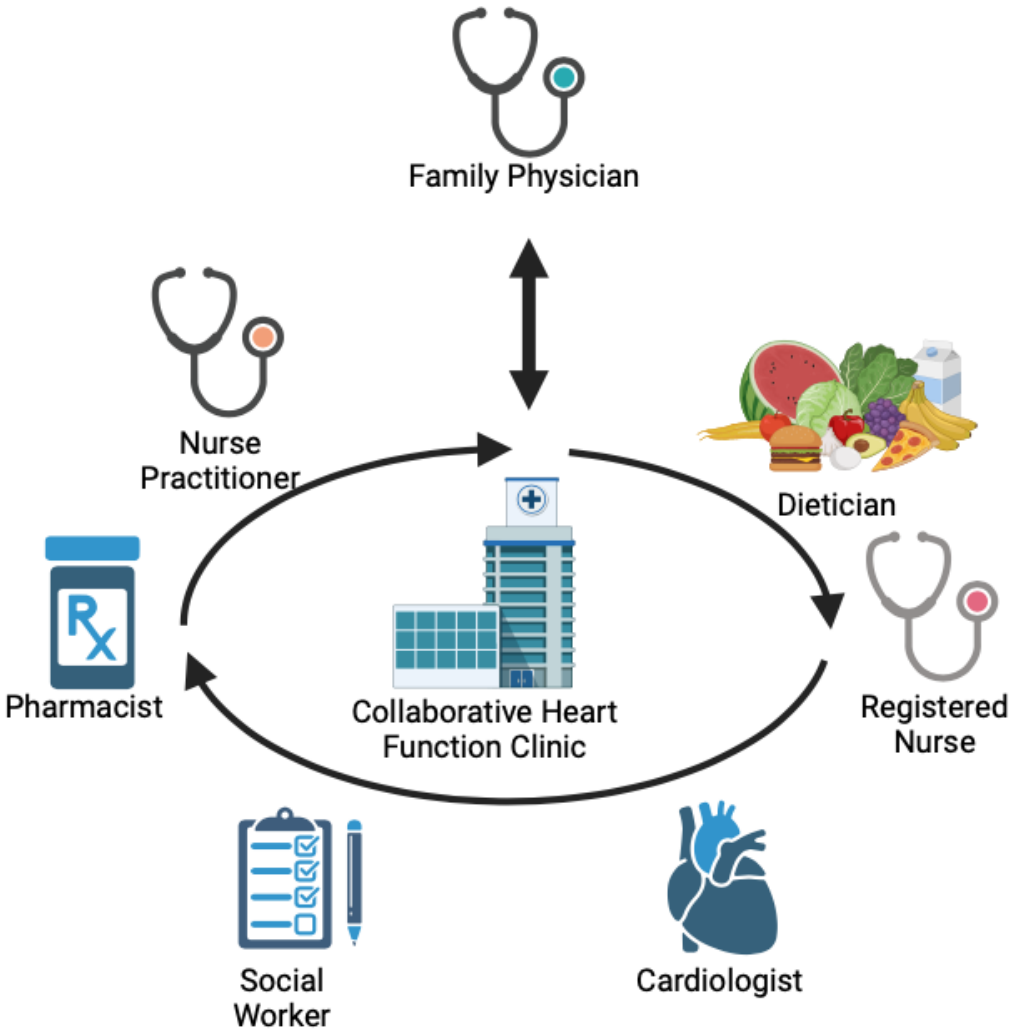
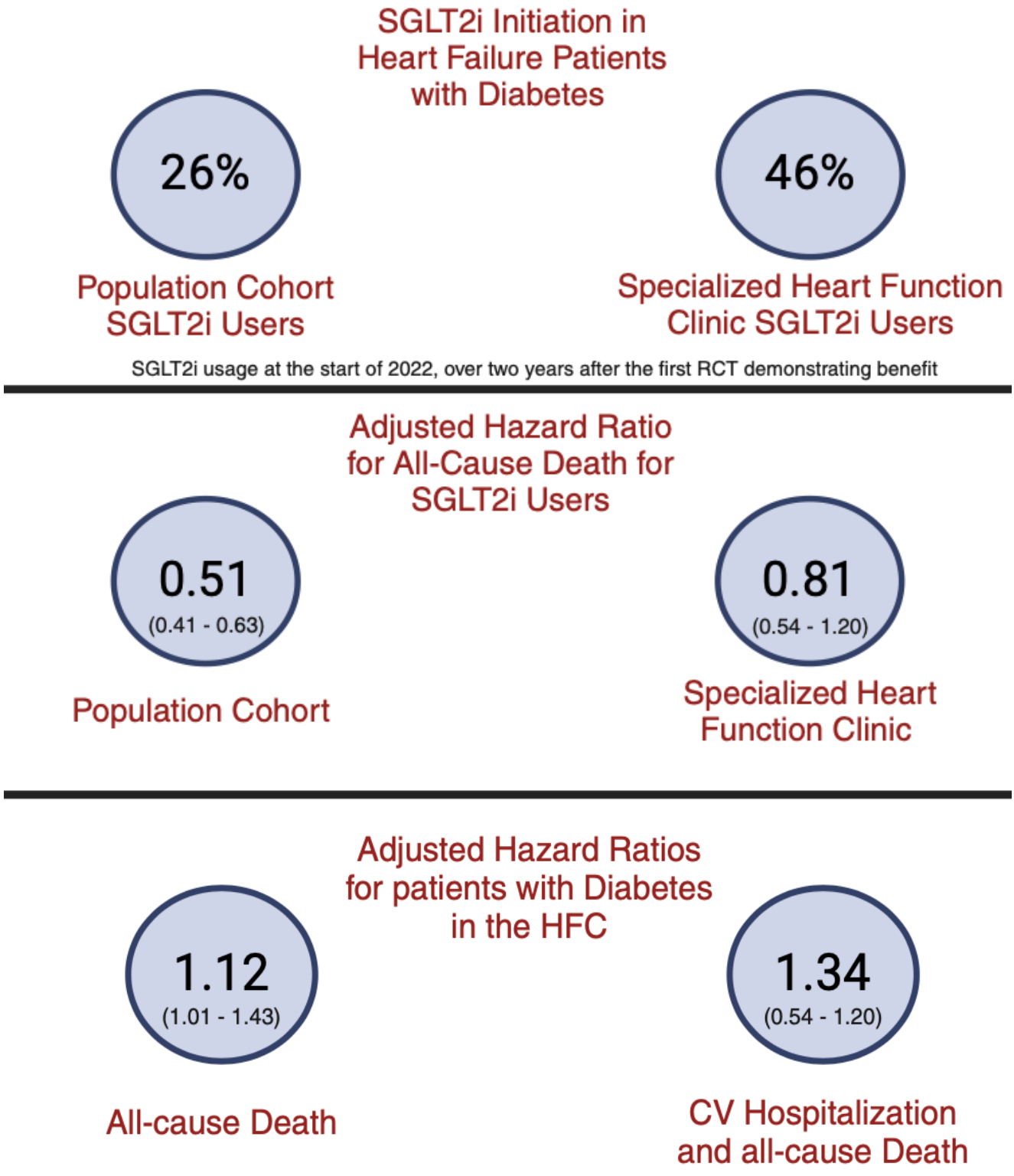


Figure 21: Summary of Results



Our HFC exhibits better attainment of GDMT in DM patients with HFrEF compared to recent reports in the literature; for example, utilization of beta-blocker (94% vs 73.4%), ACEi/ARB/ARNI (93% vs 55.9%) and MRA (82% vs 13.8%) all being substantially higher than reported by Grewal *et al*.[48] Even when comparing to other HFCs, our clinic achieved higher utilization in all patients than that reported by Dunlay *et al*.[49]; for example, utilization of beta-blocker (96.2% vs 61.8%), ACEi/ARB/ARNI (94.2% vs 84.9%) and MRA (81.8% vs 22.7%). Due to the timeframe of both trials, neither reported SGLT2 inhibitor utilization. Interestingly, in our cohort, there was still a large utilization of GDMT in patients with HFpEF and HFmrEF, which may be due to recovered EF and other comorbidities, such as hypertension, atrial fibrillation, and coronary artery disease.

The use of SGLT2 inhibitors as a cornerstone GDMT in patients with HF has been well-established in recent clinical trials.[22-25, 47, 50, 51] In this study, we found a lower uptake of SGLT2 inhibitors in patients with HF and DM treated in the community compared to a specialized heart function clinic, likely attributable to several factors. Specialized clinics utilize a multi-disciplinary approach to help with prescribing, patient education, and monitoring/follow-up. In Alberta, towards the end of this study period in March 2022, there was a special authorization process for publicly funded SGLT2 inhibitor prescriptions, and only those patients who met the specific coverage criteria were eligible (LVEF less than or equal to 40% and NYHA class II or worse symptoms despite ACEi/ARB/ARNI, BB, and an MRA if tolerated). Prior to this, only patients with DM were eligible for SGLT2 inhibitors provided they have utilized metformin previously. This is important as patients are less likely to use drugs if they require out-of-pocket payment, as was the case with SGLT2 inhibitors under most circumstances during our study period.[52]

The multidisciplinary HFC team helps prevent these unnecessary prescriptions, which has been shown to prevent optimal GDMT utilization, through appropriate prescribing and de-prescribing, which individual cardiologists and family physicians may have difficulty with given the time commitment and resources this requires.[53, 54] Pharmacists play a crucial role in a HFC, and have previously been shown to have a significant reduction in hospitalizations for HF patients and increase in GDMT utilization.[55] These results are supported by a systematic review showing a significant risk reduction of HF hospitalizations for the pharmacist collaborative care group compared to directed care.[56] Collectively, these results support the benefit of having pharmacists provide collaborative care within a HFC.

Considering the impressive association with SGLT2 inhibitor usage and decreased mortality and hospitalizations at the community level, coverage for these drugs needs to be universal to enhance the use of GDMT in HF. With the uptake being almost twice as high in a specialty clinic, perhaps multi-faceted strategies targeted to healthcare professionals, patients, and policymakers to guide risk identification and raise awareness of the clinical benefits are warranted, in addition to including them in drug coverage plans. This relatively low uptake in the community setting is certainly multi-factorial. In addition to the cost of the drug and the difficulty of special authorization, there are system-wide issues, provider care issues, and patient-related factors.[57]

Primary care teams (family physicians) who work in very busy clinics often face a heavy clinical workload. Prescribing GDMT can be very challenging to take the time to acknowledge the need, explain the rationale to the patient, provide routine follow-up laboratory work, and facilitate

drug up-titration. With our current workforce in Canada, this is not always feasible. These appointments often take specialists and the multi-disciplinary team upwards of one hour, which is impossible in the primary care setting. Additionally, education to primary care providers about these medications is often limited. These are well known barriers that need to be assessed to ensure ideal care for all.[58] Advocating for universal coverage of these lifesaving medications in addition to ongoing education is something that is necessary to increase utilization at the population level. The benefit of comprehensive care in HFC has previously been shown to not be evident early on (three-month point), which emphasizes the HFC benefits patients via longitudinal care and ongoing interventions.[59]

Risk predictors for heart failure hospitalization in patients with diabetes do not commonly take under consideration ethnicity, education, or geographical location which is very important as these factors have a large impact on patient health and outcomes.[60] Patients who inhabit deprived neighborhoods are less likely to see a cardiologist whereas patients with higher socio-economic status are more likely to attend specialized HF clinic appointments.[61] Newly-diagnosed HF patients residing in more deprived neighbourhoods had worse outcomes and reduced access to care than those less deprived.[62] In terms of cardiac disease, readmissions are known to be increased in more rural settings compared to urban settings, likely in-part related to the quality of post-acute transitional care, something that the HFC is currently only able to support in an urban setting.[63] These are likely confounding reasons for the difference in outcomes between the population cohort and the HFC cohort.

Our results are consistent with observational population-based data in Ontario, Canada, as 20.1% of patients with indications for SGLT2 inhibitors (DM and atherosclerotic CV disease) were prescribed an SGLT2 inhibitor by March 2020.[64] For Albertans aged 65 or older, SGLT2 inhibitors are only covered under limited circumstances and up until recently, no generic option was available. Before March 2022, the most common way providers could get SGLT2 inhibitors covered for patients was as an add-on therapy for T2DM after a sufficient trial of metformin and sulfonylurea when insulin is not an option. Given the recent endorsement by clinical practice guidelines for using SGLT2 inhibitors in all HF phenotypes and the substantial outcome improvement, the relative lack of up-titration of SGLT2 inhibitors is concerning.

Our findings emphasize the benefit of recommendations for GDMT implementation using multi-disciplinary titration clinics. This can be difficult in large geographical areas with low population density, which stresses the importance of in-hospital initiation/up-titration and virtual medicine especially given the disparities observed in GDMT utilization between rural and urban patients.[65] The fact that the prescription rates of other HF GDMT medications were much higher in the HFC cohort than the population cohort with concomitantly lower event rates could explain why the statistically significant association between SGLT2 inhibitor use and lower mortality seen in the population-based cohort was not replicated with the HFC cohort. Accordingly, we have previously demonstrated within our HFC cohort that the ability to up-titrate GDMT towards the maximum recommended daily dose is linked to reverse cardiac remodelling and improved long-term survival.[66] This has also been shown by *Crosier et al.* that increase in GDMT intensity is beneficial and results in lower mortality in patients with ischemic heart failure both preserved and reduced EF.[67] The combination of a ceiling effect and closer follow-up with a specialized

multidisciplinary HF team suggest that SGLT2 inhibitors may have a smaller incremental benefit in more medically optimized patients.

Diabetes was shown to have worse outcomes for HF patients when compared to no diabetes. This is likely multi-factorial, but in part related to the complications of diabetes from vascular disease and worse renal outcomes. Patients with diabetes in our cohort were more likely to have CKD and their etiology of HF was more commonly ischemic in nature. Additionally, DM is thought to also precipitate or worsen HF through oxidative stress and high inflammatory states, consistent with the worse outcomes demonstrated here.[34]

The end point of CV hospitalization or mortality may be strongly driven by mortality alone. This endpoint was selected as to make it clear that both CV hospitalizations and mortality were taken into consideration, and considering CV hospitalization alone there is concern that this would likely be confounded by mortality. There is growing evidence that SGLT2 inhibitors may have anti-arrhythmogenic effects, specifically regarding ventricular arrhythmias and adverse electrical remodeling [68], and patients with HF prescribed SGLT2 inhibitors had a significant difference in mortality, but a non-statistical significance in HF hospitalization. Our results are consistent with these findings, showing a greater impact on overall mortality than CV hospitalization/death.

The HFC cohort had a lower SGLT2 inhibitor discontinuation rate than the provincial cohort and those reported by the EUCLID study, which was 28.1% over a median follow-up of 42 months.[69] At the HFC, physicians, pharmacists, and nurse practitioners can provide patients with the rationale for continuing the drugs and ensure these lifesaving medications are only stopped

with good reason. We found that 64% of patients with HF and DM in Alberta met RCT trial eligibility criteria for SGLT2 inhibitor, similar to other populational estimates of about 69%.[70] The patients that met this criteria (cohort 2) had impressive results, showing even greater survival benefits then those overserved in the combined cohort (cohort 1) and many of the RCTs. This clearly validates the benefits of these therapies in a large populational cohort. Even when considering the group not eligible (cohort 3) there was still a mortality benefit from SGLT2 inhibitor usage, suggesting that further research to expand the SGLT2 inhibitor eligible population is warranted.

In the contemporary era, SGLT2 inhibitors should be prescribed to individuals with HF irrespective of their DM status. Unfortunately, due to the lack of drug coverage for SGLT2 inhibitors for patients without DM for the majority of this study time period in Alberta, we saw very little utilization, and as such, we focused on the individuals with HF and DM. With time, there will inevitably be further initiation of SGLT2 inhibitors and an increase in user sample size, allowing for further analyses. It should be noted that our population-based cohort estimates are based on drug dispensations, which underestimates prescriptions given primary non-adherence (failure to fill the first prescription), which can be as high as 9% for CV drugs in contemporary Canadian data.[71] Moreover, there are many un-measured social and structural factors that will cause inherent bias in rates of SGLT2 inhibitor uptake, such as patients are more likely to receive SGLT2 inhibitor prescription with higher socio-economic status. Additionally, due to the nature of population-based cohort data, we were unable to perform individual chart review, and determine the exact rationale for discontinuation or specific drug-related adverse events. Lastly, for the population-based cohort, we required patients to have an echocardiogram result to classify them

according to ejection fraction, which could potentially cause a selection bias for those with access to tertiary care centers.

The current analysis is limited by its observational nature. The improved survival amongst SGLT2 inhibitor users, specifically in the population cohort is likely multi-factorial in addition to the SGLT2 inhibitor itself. There are many un-measured social and structural factors that will cause bias inherently, such as patients more likely to get SGLT2 inhibitors may have higher socio-economic status. Additionally, a limitation for the population cohort is that an echocardiogram was required at a tertiary care centre, which is likely an explanation for the limited rural residence of patients. In terms of co-morbidities, the dataset used did not have claims data, which may also limit accuracy in terms of baseline information.

Conclusion

This study confirms that the benefits of SGLT2 inhibitors reported in RCTs are also seen in clinical practice for patients with HF and DM. However, we demonstrated substantial under-utilization of SGLT2 inhibitors in HF patients with DM, even in those followed in a specialty HF clinic. Given the evidence and clinical practice guidelines reflecting SGLT2 inhibitors as first line for HF, there is an ongoing need for innovative strategies to optimize uptake of guideline-directed therapy in the community.

This study showcases that even with high rates of GDMT utilization in a contemporary specialized clinic, patients with concomitant HF and DM continues to experience poorer QOL and worse outcomes than HF patients without DM.

References

1. Gagnon LR, Hazra D, Perera K, et al. Uptake of SGLT2i and Outcomes in Patients with Diabetes and Heart Failure: A Population-Based Cohort and a Specialized Clinic Cohort. *American Heart Journal.* 2024.

2. Ziaeian B, Hernandez AF, DeVore AD, et al. Long-term outcomes for heart failure patients with and without diabetes: From the Get With The Guidelines-Heart Failure Registry. *Am Heart J.* 2019;211:1-10.

3. Dei Cas A, Khan SS, Butler J, et al. Impact of diabetes on epidemiology, treatment, and outcomes of patients with heart failure. *JACC Heart Fail.* 2015;3:136-145.

4. McDonald M, Virani S, Chan M, et al. CCS/CHFS Heart Failure Guidelines Update: Defining a New Pharmacologic Standard of Care for Heart Failure With Reduced Ejection Fraction. *Can J Cardiol.* 2021;37:531-546.

5. Velliou M, Polyzogopoulou E, Ventoulis I, Parissis J. Clinical pharmacology of SGLT-2 inhibitors in heart failure. *Expert Review of Clinical Pharmacology.* 2023;16:149-160.

6. Ni L, Yuan C, Chen G, Zhang C, Wu X. SGLT2i: beyond the glucose-lowering effect. *Cardiovascular Diabetology.* 2020;19:98.

7. Ghezzi C, Yu AS, Hirayama BA, et al. Dapagliflozin Binds Specifically to Sodium-Glucose Cotransporter 2 in the Proximal Renal Tubule. *J Am Soc Nephrol.* 2017;28:802-810.

8. Anker SD, Butler J. Empagliflozin, calcium, and SGLT1/2 receptor affinity: another piece of the puzzle. *ESC Heart Fail.* 2018;5:549-551.

9. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *New England Journal of Medicine.* 2015;373:2117-2128.

10. Yang Y, Zhao C, Ye Y, Yu M, Qu X. Prospect of Sodium-Glucose Co-transporter 2 Inhibitors Combined With Insulin for the Treatment of Type 2 Diabetes. *Front Endocrinol (Lausanne).* 2020;11:190.

11. Kario K, Ferdinand KC, O'Keefe JH. Control of 24-hour blood pressure with SGLT2 inhibitors to prevent cardiovascular disease. *Progress in Cardiovascular Diseases.* 2020;63:249-262.

12. KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease. *Kidney Int.* 2022;102:S1-s127.

13. Chen S, Coronel R, Hollmann MW, Weber NC, Zuurbier CJ. Direct cardiac effects of SGLT2 inhibitors. *Cardiovascular Diabetology.* 2022;21:45.

14. Ansary TM, Nakano D, Nishiyama A. Diuretic Effects of Sodium Glucose Cotransporter 2 Inhibitors and Their Influence on the Renin-Angiotensin System. *Int J Mol Sci.* 2019;20.

15. Yaribeygi H, Lhaf F, Sathyapalan T, Sahebkar A. Effects of novel antidiabetes agents on apoptotic processes in diabetes and malignancy: Implications for lowering tissue damage. *Life Sciences.* 2019;231:116538.

16. Lee T-M, Chang N-C, Lin S-Z. Dapagliflozin, a selective SGLT2 Inhibitor, attenuated cardiac fibrosis by regulating the macrophage polarization via STAT3 signaling in infarcted rat hearts. *Free Radical Biology and Medicine.* 2017;104:298-310.

17. Yurista SR, Nguyen CT, Rosenzweig A, de Boer RA, Westenbrink BD. Ketone bodies for the failing heart: fuels that can fix the engine? *Trends Endocrinol Metab.* 2021;32:814-826.

18. Qiu H, Novikov A, Vallon V. Ketosis and diabetic ketoacidosis in response to SGLT2 inhibitors: Basic mechanisms and therapeutic perspectives. *Diabetes Metab Res Rev.* 2017;33.

19. Staels B. Cardiovascular Protection by Sodium Glucose Cotransporter 2 Inhibitors: Potential Mechanisms. *Am J Med.* 2017;130:S30-s39.

20. Saucedo-Orozco H, Voorrips SN, Yurista SR, de Boer RA, Westenbrink BD. SGLT2 Inhibitors and Ketone Metabolism in Heart Failure. *J Lipid Atheroscler.* 2022;11:1-19.

21. Kato ET, Silverman MG, Mosenzon O, et al. Effect of Dapagliflozin on Heart Failure and Mortality in Type 2 Diabetes Mellitus. *Circulation.* 2019;139:2528-2536.

22. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *New England Journal of Medicine.* 2019;381:1995-2008.

23. Packer M, Anker SD, Butler J, et al. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *New England Journal of Medicine.* 2020;383:1413-1424.

24. Anker SD, Butler J, Filippatos G, et al. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *New England Journal of Medicine.* 2021;385:1451-1461.

25. Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. *New England Journal of Medicine.* 2022;387:1089-1098.

26. Lorenzo M, Miñana G, Palau P, et al. Short-term Changes in Hemoglobin and Changes in Functional Status, Quality of Life and Natriuretic Peptides After Initiation of Dapagliflozin in Heart Failure With Reduced Ejection Fraction. *J Card Fail.* 2023;29:849-854.

27. McCoy RG, Herrin J, Swarna KS, et al. Effectiveness of glucose-lowering medications on cardiovascular outcomes in patients with type 2 diabetes at moderate cardiovascular risk. *Nature Cardiovascular Research.* 2024;3:431-440.

28. Nagendran J, Oudit GY, Bakal JA, Light PE, Dyck JR, McAlister FA. Are users of sulphonylureas at the time of an acute coronary syndrome at risk of poorer outcomes? *Diabetes Obes Metab.* 2013;15:1022-1028.

29. Ashcroft FM. Mechanisms of the glycaemic effects of sulfonylureas. *Horm Metab Res.* 1996;28:456-463.

30. Wang MT, Huang YL, Lai JH, et al. Association Between Specificity of Sulfonylureas to Cardiac Mitochondrial KATP Channels and the Risk of Major Adverse Cardiovascular Events in Type 2 Diabetes. *Diabetes Care.* 2022;45:1276-1287.

31. Wilding JPH, Batterham RL, Calanna S, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. *N Engl J Med.* 2021;384:989-1002.

32. Kosiborod MN, Abildstrøm SZ, Borlaug BA, et al. Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity. *N Engl J Med.* 2023;389:1069-1084.

33. Holman RR, Bethel MA, Mentz RJ, et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med.* 2017;377:1228-1239.

34. Rosenstock J, Kahn SE, Johansen OE, et al. Effect of Linagliptin vs Glimepiride on Major Adverse Cardiovascular Outcomes in Patients With Type 2 Diabetes: The CAROLINA Randomized Clinical Trial. *JAMA.* 2019;322:1155-1166.

35. Venniyoor A. Tirzepatide Once Weekly for the Treatment of Obesity. *N Engl J Med.* 2022;387:1433-1434.

36. Packer M. Do DPP-4 Inhibitors Cause Heart Failure Events by Promoting Adrenergically Mediated Cardiotoxicity? *Circulation Research.* 2018;122:928-932.

37. Vörös I, Onódi Z, Tóth V, et al. Saxagliptin Cardiotoxicity in Chronic Heart Failure: The Role of DPP4 in the Regulation of Neuropeptide Tone. *Biomedicines.* 2022;10.

38. Scirica BM, Braunwald E, Raz I, et al. Heart Failure, Saxagliptin, and Diabetes Mellitus: Observations from the SAVOR-TIMI 53 Randomized Trial. *Circulation.* 2014;130:1579-1588.

39. Xia C, Goud A, D'Souza J, et al. DPP4 inhibitors and cardiovascular outcomes: safety on heart failure. *Heart Fail Rev.* 2017;22:299-304.

40. Thorvaldsen T, Ferrannini G, Mellbin L, et al. Eligibility for Dapagliflozin and Empagliflozin in a Real-world Heart Failure Population. *J Card Fail.* 2022;28:1050-1062.

41. Nguyen Q, Wang K, Nikhanj A, et al. Screening and Initiating Supportive Care in Patients With Heart Failure. *Front Cardiovasc Med.* 2019;6:151.

42. Quan H, Li B, Saunders LD, et al. Assessing validity of ICD-9-CM and ICD-10 administrative data in recording clinical conditions in a unique dually coded database. *Health Serv Res.* 2008;43:1424-1441.

43. Pampalon R, Hamel D, Gamache P. Health inequalities in urban and rural Canada: comparing inequalities in survival according to an individual and area-based deprivation index. *Health Place.* 2010;16:416-420.

44. Zhou Z, Rahme E, Abrahamowicz M, Pilote L. Survival bias associated with time-to-treatment initiation in drug effectiveness evaluation: a comparison of methods. *Am J Epidemiol.* 2005;162:1016-1023.

45. Arnold SV, Khunti K, Bonnet F, et al. Type 2 diabetes and heart failure: insights from the global DISCOVER study. *ESC Heart Fail.* 2021;8:1711-1716.

46. Marx N, Federici M, Schütt K, et al. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. *Eur Heart J.* 2023;44:4043-4140.

47. McDonagh TA, Metra M, Adamo M, et al. 2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J.* 2023;44:3627-3639.

48. Grewal D, Partow-Navid R, Garcia D, et al. Role of Guideline Directed Medical Therapy Doses and Optimization in Patients Hospitalized With Decompensated Systolic Heart Failure. *Am J Cardiol.* 2021;151:64-69.

49. Dunlay SM, Killian JM, Roger VL, et al. Guideline-Directed Medical Therapy in Newly Diagnosed Heart Failure With Reduced Ejection Fraction in the Community. *J Card Fail.* 2022;28:1500-1508.

50. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. *European Heart Journal.* 2021;42:3599-3726.

51. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 American College of Cardiology/American Heart Association/Heart Failure Society of America Guideline for the Management of Heart Failure: Executive Summary. *J Card Fail.* 2022;28:810-830.

52. Luo J, Feldman R, Callaway Kim K, et al. Evaluation of Out-of-Pocket Costs and Treatment Intensification With an SGLT2 Inhibitor or GLP-1 RA in Patients With Type 2 Diabetes and Cardiovascular Disease. *JAMA Netw Open.* 2023;6:e2317886.

53. Khan MS, Singh S, Segar MW, et al. Polypharmacy and Optimization of Guideline-Directed Medical Therapy in Heart Failure. *JACC: Heart Failure.* 2023;11:1507-1517.

54. Sharma A, Verma S, Bhatt DL, et al. Optimizing Foundational Therapies in Patients With HFrEF: How Do We Translate These Findings Into Clinical Care? *JACC Basic Transl Sci.* 2022;7:504-517.

55. Patil T, Ali S, Kaur A, et al. Impact of Pharmacist-Led Heart Failure Clinic on Optimization of Guideline-Directed Medical Therapy (PHARM-HF). *J Cardiovasc Transl Res.* 2022;15:1424-1435.

56. Koshman SL, Charrois TL, Simpson SH, McAlister FA, Tsuyuki RT. Pharmacist Care of Patients With Heart Failure: A Systematic Review of Randomized Trials. *Archives of Internal Medicine.* 2008;168:687-694.

57. Majumdar SR, McAlister FA, Furberg CD. From knowledge to practice in chronic cardiovascular disease: a long and winding road. *J Am Coll Cardiol.* 2004;43:1738-1742.

58. Gao Y, Peterson E, Pagidipati N. Barriers to prescribing glucose-lowering therapies with cardiometabolic benefits. *Am Heart J.* 2020;224:47-53.

59. Van Spall HGC, Lee SF, Xie F, et al. Effect of Patient-Centered Transitional Care Services on Clinical Outcomes in Patients Hospitalized for Heart Failure: The PACT-HF Randomized Clinical Trial. *Jama.* 2019;321:753-761.

60. Razaghizad A, Oulousian E, Randhawa VK, et al. Clinical Prediction Models for Heart Failure Hospitalization in Type 2 Diabetes: A Systematic Review and Meta-Analysis. *Journal of the American Heart Association.* 2022;11:e024833.

61. Abdel-Qadir H, Akioyamen LE, Fang J, et al. Association of Neighborhood-Level Material Deprivation With Atrial Fibrillation Care in a Single-Payer Health Care System: A Population-Based Cohort Study. *Circulation.* 2022;146:159-171.

62. Bobrowski D, Dorovenis A, Abdel-Qadir H, et al. Association of neighbourhood-level material deprivation with adverse outcomes and processes of care among patients with heart failure in a single-payer healthcare system: A population-based cohort study. *Eur J Heart Fail.* 2023;25:2274-2286.

63. Donio PJ, Freitas C, Austin PC, et al. Comparison of Readmission and Death Among Patients With Cardiac Disease in Northern vs Southern Ontario. *Can J Cardiol.* 2019;35:341-351.

64. Ozaki AF, Ko DT, Chong A, et al. Prescribing patterns and factors associated with sodium-glucose cotransporter-2 inhibitor prescribing in patients with diabetes mellitus and atherosclerotic cardiovascular disease. *CMAJ Open.* 2023;11:E494-e503.

65. Mentias A, Keshvani N, Sumarsono A, et al. Patterns, Prognostic Implications, and Rural-Urban Disparities in Optimal GDMT Following HFrEF Diagnosis Among Medicare Beneficiaries. *JACC: Heart Failure.* 2023;0.

66. Wang K, Youngson E, Bakal JA, Thomas J, McAlister FA, Oudit GY. Cardiac reverse remodelling and health status in patients with chronic heart failure. *ESC Heart Fail.* 2021;8:3106-3118.

67. Crosier R, Austin PC, Ko DT, et al. Intensity of Guideline-Directed Medical Therapy for Coronary Heart Disease and Ischemic Heart Failure Outcomes. *Am J Med.* 2021;134:672-681.e674.

68. Curtain JP, Docherty KF, Jhund PS, et al. Effect of dapagliflozin on ventricular arrhythmias, resuscitated cardiac arrest, or sudden death in DAPA-HF. *Eur Heart J.* 2021;42:3727-3738.

69. Weissler EH, Mulder H, Rockhold FW, et al. Understanding Study Drug Discontinuation Through EUCLID. *Front Cardiovasc Med.* 2022;9:947645.

70. Bassi NS, Ziaeian B, Yancy CW, Fonarow GC. Association of Optimal Implementation of Sodium-Glucose Cotransporter 2 Inhibitor Therapy With Outcome for Patients With Heart Failure. *JAMA Cardiology.* 2020;5:948-951.

71. Zeitouny S, Cheng L, Wong ST, Tadrous M, McGrail K, Law MR. Prevalence and predictors of primary nonadherence to medications prescribed in primary care. *Cmaj.* 2023;195:E1000-e1009.

Appendix

KCCQ-12 Questionnaire

Kansas City Cardiomyopathy Questionnaire (KCCQ-12)

The following questions refer to your **heart failure** and how it may affect your life. Please read and complete the following questions. There are no right or wrong answers. Please mark the answer that best applies to you.

1. **Heart failure** affects different people in different ways. Some feel shortness of breath while others feel fatigue. Please indicate how much you are limited by **heart failure** (shortness of breath or fatigue) in your ability to do the following activities over the past 2 weeks.

Activity	**Extremely** Limited	**Quite a bit** Limited	**Moderately** Limited	**Slightly** Limited	**Not at all** Limited	Limited for other reasons or did not do the activity
a. Showering/bathing	O	O	O	O	O	O
b. Walking 1 block on level ground	O	O	O	O	O	O
c. Hurrying or jogging (as if to catch a bus)	O	O	O	O	O	O
	1	2	3	4	5	6

2. Over the past 2 weeks, how many times did you have **swelling** in your feet, ankles or legs when you woke up in the morning?

Every morning	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
O	O	O	O	O
1	2	3	4	5

3. Over the past 2 weeks, on average, how many times has **fatigue** limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
O	O	O	O	O	O	O
1	2	3	4	5	6	7

4. Over the past 2 weeks, on average, how many times has **shortness of breath** limited your ability to do what you wanted?

All of the time	Several times per day	At least once a day	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
O	O	O	O	O	O	O
1	2	3	4	5	6	7

5. Over the past 2 weeks, on average, how many times have you been forced to sleep sitting up in a chair or with at least 3 pillows to prop you up because of **shortness of breath**?

Every night	3 or more times per week but not every day	1-2 times per week	Less than once a week	Never over the past 2 weeks
O	O	O	O	O
1	2	3	4	5

6. Over the past 2 weeks, how much has your **heart failure** limited your enjoyment of life?

It has **extremely** limited my enjoyment of life	It has limited my enjoyment of life **quite a bit**	It has **moderately** limited my enjoyment of life	It has **slightly** limited my enjoyment of life	It has **not limited** my enjoyment of life at all
O	O	O	O	O
1	2	3	4	5

7. If you had to spend the rest of your life with your **heart failure** the way it is right now, how would you feel about this?

Not at all satisfied	Mostly dissatisfied	Somewhat satisfied	Mostly satisfied	Completely satisfied
O	O	O	O	O
1	2	3	4	5

8. How much does your **heart failure** affect your lifestyle? Please indicate how your **heart failure** may have limited your participation in the following activities over the past 2 weeks.

Activity	**Severely** Limited	Limited **quite a bit**	**Moderately** limited	**Slightly** limited	**Did not** limit at all	Does not apply or did not do for other reasons
a. Hobbies, recreational activities	O	O	O	O	O	O
b. Working or doing household chores	O	O	O	O	O	O
c. Visiting family or friends out of your home	O	O	O	O	O	O
	1	2	3	4	5	6