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SGLT-2 inhibitors across competing pathways of type 2 diabetes, chronic kidney disease and heart failure

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Renal, Respiratory and Allergy Expert Advisory Group for the CHM. She is a paid advisor to the National Institute for Health and Care Excellence. KRA is a member of the National Institute for Health and Care Excellence (NICE) Diagnostics Advisory Committee, the NICE Decision and Technical Support Units, and is a National Institute for Health Research (NIHR) Senior Investigator Emeritus [NF-SI-0512-10159]. He has served as a paid consultant, providing unrelated methodological and strategic advice, to the pharmaceutical and life sciences industry generally, as well as to DHSC/NICE, and has received unrelated research funding from Association of the British Pharmaceutical Industry (ABPI), European Federation of Pharmaceutical Industries & Associations (EFPIA), Pfizer, Sanofi and Swiss Precision Diagnostics/Clearblue. He has also received course fees from ABPI and the University of Bristol, and is a founding Partner and Director of Visible Analytics Limited, a health technology assessment consultancy company, and is currently its Chief Statistical & HTA Adviser.

Abstract

Type 2 diabetes, chronic kidney disease and heart failure commonly co-exist, yet multi-indication therapies such as sodium-glucose co-transporter-2 (SGLT-2) inhibitors are appraised one indication at a time. Here we combine multi-state models evaluating the natural history of disease including the order in which these conditions accrue, fitted to linked electronic health records for 1.3 million adults in Wales, with treatment effects from randomised controlled trials in a patient-level simulation. Among people diagnosed with at least one of the three conditions, SGLT-2 inhibitors increase mean life expectancy by 1.81 years (95% CI: 0.96, 2.73) compared with standard of care, and delay a subsequent diagnosis of type 2 diabetes by up to 3.09 (95% CI: 1.42, 4.80) years, with the longest delays in people living with both chronic kidney disease and heart failure. In people with type 2 diabetes, treatment reduces the risks of developing chronic kidney disease and heart failure more than the risk of death, so more people die without a further diagnosis; reductions in individual transitions therefore do not translate proportionately into gains in life expectancy. Evaluating multi-indication therapies across whole disease pathways, rather than single conditions, could better inform health policy for people living with multiple long-term conditions.

Introduction

Multiple long-term conditions (MLTC), or multimorbidity, is defined as the coexistence of two or more long-term health conditions in an individual[1], and results in decreased quality of life, functional decline, increased healthcare utilisation (including emergency hospital admissions)[2], polypharmacy, increased treatment burden, and increased mortality[3,4]. The burden associated with MLTC on both the patient and health service provider intensifies with increased numbers of coexisting long-term conditions[5,6]. Health and social care costs for people with MLTC exceed what would be expected from simply summing the costs of managing each component condition alone, with total costs approximately doubling for each additional long-term condition[6–8].

Multiple long-term conditions have profound implications for health service providers internationally[9]. Health services are typically structured to deliver condition- or specialty-specific healthcare provision, with reimbursement agencies such as the National Institute for Health and Care Excellence (NICE) in the UK focusing on developing clinical and cost-effective recommendations in single conditions[10]. However, for individuals living with MLTC, standardised care for each long-term condition independently can be inappropriate[11,12]. For example, condition-specific prescribing in MLTC can lead to treatment burden and unnecessary polypharmacy, resulting in an increased risk of potential drug-drug interactions and associated adverse events[13]. This risk increases with increasing numbers of co-existing conditions and numbers of prescribed treatments[14]. As a result of such conflicts, people living with MLTC may have fewer treatment options for the management of each of their component conditions.

Targeted approaches for the management of MLTC have been identified as a crucial component of future healthcare planning[15], including further research focussing on providing evidence for models of care in MLTC[16,17]. Treatments that can be used in multiple conditions, known as multi-indication therapies, have the potential to play a central role in the adoption of a holistic and targeted approach to healthcare management in MLTC.

The Sodium-Glucose Cotransporter-2 (SGLT-2) inhibitors are examples of multi-indication therapies. SGLT-2 inhibitors act on the proximal tubule of the kidney, where SGLT-2 is responsible for most of the reabsorption of filtered glucose. By blocking this transporter, they increase urinary glucose excretion and lower blood glucose

independently of insulin, while also promoting sodium excretion and a mild osmotic diuresis that reduce blood pressure and fluid volume; their cardiac and kidney benefits extend to people without diabetes, suggesting mechanisms beyond glucose lowering. However, individual SGLT-2 inhibitors vary in the breadth of their marketing authorisation. Dapagliflozin and empagliflozin are each licensed in the UK and Europe for glycaemic control in type 2 diabetes mellitus (T2DM), chronic heart failure (HF), and chronic kidney disease (CKD). By contrast, canagliflozin and ertugliflozin remain licensed for T2DM only. In the UK, NICE recommendations are generally restricted to a technology's marketing authorisation unless the Department of Health and Social Care specifically indicates otherwise. Between 2013 and 2019, NICE recommended the use of dapagliflozin, canagliflozin, empagliflozin and ertugliflozin as combination therapy with metformin for treating hyperglycaemia in T2DM[18–21] and as monotherapies,[18,22] in people who are contraindicated or cannot take metformin. In 2026, NICE guidelines for T2DM recommended the use of dapagliflozin, because it is the least expensive of the available options[23]. Between 2021 and 2023, dapagliflozin[24] and empagliflozin[25] were approved for use in chronic heart failure (HF) with reduced ejection fraction in adults as an add on to optimised standard care, or with preserved or mildly reduced ejection fraction[26,27], as well as in CKD[28,29].

It is well documented that T2DM, HF, and CKD commonly co-exist[30], and thus consideration of a modelling framework to estimate the clinical effectiveness of SGLT-2 inhibitors compared to standard of care (SOC) across all three indications, including people living with more than one of these conditions, has the potential to reduce polypharmacy, drug-drug interactions, and associated costs.

Motivated by recent NICE recommendations on the use of SGLT-2 inhibitors in these three commonly co-existing long-term conditions: T2DM[18–22], HF[24–27], and CKD[28,29], and with current guidance recommending dapagliflozin for treating T2DM as the cheapest SGLT-2 inhibitor[23], the objective of this study was to develop a modelling framework to estimate the effect of SGLT-2 inhibitors as multi-indication therapies (using dapagliflozin as the exemplar) in people living with one or more of T2DM, CKD, and HF, by applying patient-level simulation to population-scale, linked, electronic health records.

Results

We fitted a multi-state model of the order in which T2DM, CKD and HF accrue to linked electronic health records for 1,311,822 people in Wales who were free of all three conditions on 1 January 2000 (Fig. 1), and combined the estimated transition hazards with treatment effects from randomised controlled trials in a patient-level simulation comparing SGLT-2 inhibitors with standard of care (SOC) (see Methods).

Natural History of Disease Model

The multi-state model was derived from 1,311,822 individuals free of T2DM, CKD, and HF at cohort entry [the index condition-free (ICF) population], with a median age of 45 years (IQR 35 to 57) and an approximately even distribution across WIMD deprivation quintiles (18 to 21% per quintile) and sex (48% male, 52% female) (Table 1). Over the follow-up period, 67,894 individuals progressed to CKD as their first condition, 41,934 to T2DM, and 40,034 to HF (Fig. 2), with progressively older median ages at these single-condition states (CKD = 62 years (IQR: 52–70), T2DM = 52 years (IQR: 43–61), and HF = 63 years (IQR: 52–74)) reflecting the differing typical ages of onset for each condition.

Table 1
Population characteristics by transition from natural history of disease model

Health state	n	Median age (IQR),	Welsh Index Multiple Deprivation Quintile, n (proportion)					Sex, n (proportion)	
		years	1st (Most Deprived)	2nd	3rd	4th	5th (Least Deprived)	Male	Female
ICF	1311822	45 (35–57)	268587 (0.20)	263330 (0.20)	269905 (0.21)	239578 (0.18)	270422 (0.21)	633748 (0.48)	678074 (0.52)
CKD	67894	62 (52–70)	14428 (0.21)	14037 (0.21)	14845 (0.22)	12685 (0.19)	11899 (0.18)	27683 (0.41)	40211 (0.59)
T2DM	41934	52 (43–61)	10531 (0.25)	9255 (0.22)	8429 (0.20)	6941 (0.17)	6778 (0.16)	23555 (0.56)	18379 (0.44)
HF	40034	63 (52–74)	7896 (0.20)	8099 (0.20)	8400 (0.21)	7480 (0.19)	8159 (0.20)	19517 (0.49)	20517 (0.51)
CKD-T2DM	3590	64 (55–71)	949 (0.26)	824 (0.23)	731 (0.20)	558 (0.16)	528 (0.15)	1731 (0.48)	1859 (0.52)
CKD-HF	4130	71 (63–79)	830 (0.20)	829 (0.20)	950 (0.23)	755 (0.18)	766 (0.19)	1774 (0.43)	2356 (0.57)
T2DM-CKD	3867	63 (55–70)	951 (0.25)	879 (0.23)	792 (0.20)	675 (0.17)	570 (0.15)	1887 (0.49)	1980 (0.51)
T2DM-HF	1729	63 (54–72)	403 (0.23)	393 (0.23)	358 (0.21)	308 (0.18)	267 (0.15)	995 (0.58)	734 (0.42)
HF-CKD	5207	73 (65–79)	1048 (0.20)	1026 (0.20)	1145 (0.22)	985 (0.19)	1003 (0.19)	2340 (0.45)	2867 (0.55)
HF-T2DM	1676	64 (54–73)	394 (0.24)	374 (0.22)	328 (0.19)	282 (0.17)	298 (0.18)	933 (0.56)	743 (0.44)
CKD-T2DM-HF	135	70 (63–76)	32 (0.26)	23 (0.17)	35 (0.26)	20 (0.15)	25 (0.19)	61 (0.45)	74 (0.55)
CKD-HF-T2DM	155	70 (62–76)	34 (0.22)	38 (0.25)	36 (0.23)	20 (0.13)	27 (0.17)	79 (0.51)	76 (0.49)
T2DM-CKD-HF	263	70 (61–77)	59 (0.22)	64 (0.24)	45 (0.17)	55 (0.21)	40 (0.15)	127 (0.48)	136 (0.52)

ICF: Index Condition Free; CKD: Chronic Kidney Disease; T2DM: Type 2 Diabetes; HF: Heart failure.

Health state	n	Median age (IQR),	Welsh Index Multiple Deprivation Quintile, n (proportion)					Sex, n (proportion)	
		years	1st (Most Deprived)	2nd	3rd	4th	5th (Least Deprived)	Male	Female
T2DM-HF-CKD	213	72 (65–79)	48 (0.23)	58 (0.27)	42 (0.20)	45 (0.21)	20 (0.09)	108 (0.51)	105 (0.49)
HF-CKD-T2DM	305	72 (64–77)	85 (0.28)	62 (0.20)	58 (0.19)	45 (0.15)	55 (0.18)	150 (0.49)	155 (0.51)
HF-T2DM-CKD	201	72 (65–77)	44 (0.22)	45 (0.22)	45 (0.22)	33 (0.16)	34 (0.17)	106 (0.53)	95 (0.47)
Death	186779	73 (63–80)	42636 (0.23)	39853 (0.21)	39319 (0.21)	32506 (0.17)	32465 (0.17)	89260 (0.48)	97519 (0.52)

ICF: Index Condition Free; CKD: Chronic Kidney Disease; T2DM: Type 2 Diabetes; HF: Heart failure.

Among individuals progressing to a second condition, the largest single-condition-to-two-condition state was CKD-HF (CKD followed by HF; n = 4,130, median age 71 (IQR: 63–79), followed by T2DM-CKD (n = 3,867) and CKD-T2DM (n = 3,590). The triple-condition states were considerably smaller, ranging from 135 individuals (CKD-T2DM-HF) to 305 (HF-CKD-T2DM), with median ages at these states clustering around 70–72 years across all six orderings. A higher proportion of individuals in the most-deprived WIMD quintile was observed in several triple-condition states (e.g. 28% in HF-CKD-T2DM and 26% in CKD-T2DM-HF and T2DM-CKD-HF) compared with the ICF population (20%), consistent with the established association between socioeconomic deprivation and accumulation of MLTC[31].

A total of 186,779 individuals (14% of the ICF cohort) died during follow-up without a recorded diagnosis of T2DM, CKD, or HF, at a median age of 73 years (IQR 63–80) as such this group provides a reference for general all-cause mortality in the cohort.

Patient-level simulation

Table 2 presents the mean differences (SGLT-2 inhibitors vs SOC) in cause-specific transition probabilities, age at transition, and life expectancy for each transition, and Fig. 3 shows the cumulative incidence of each transition by time since entering the state. Supplementary Table 1 presents transition probabilities, mean age at transition, and mean life expectancy for the SGLT-2 inhibitors and SOC simulated populations (n = 1,000,000), generated via the patient-level simulation based on the natural history model and treatment effect estimates. As SGLT-2 inhibitors are indicated only once an individual has developed T2DM, CKD, or HF, the probabilities of transitioning from ICF to CKD, T2DM, HF, or Death were identical between arms (CKD: 0.179 [95% CI: 0.179, 0.180], T2DM: 0.074 [95% CI: 0.074, 0.075], HF: 0.081 [95%CI: 0.081, 0.082], and Death: 0.665 [95%CI: 0.664, 0.666]; Supplementary Table 1). The primary outcome of downstream life expectancy, aggregated across all subsequent pathways, differed by treatment arm depending on the first condition developed: individuals developing CKD first had statistically significant higher mean life expectancy under SGLT-2 inhibitor treatment than SOC (82.12 vs 79.76 years, a difference of 2.36 years [95% CI: 0.73, 4.15]), and individuals developing HF first also had a higher mean life

expectancy under treatment (77.22 vs 76.21 years, a difference of 1.01 years [95% CI: 0.38, 1.75]). Individuals developing T2DM first showed a smaller benefit, which was not statistically significant (78.81 vs 78.05 years, a difference of 0.76 years [95% CI: -0.005, 1.65]). Across the population with one or more of T2DM, HF, and CKD, the overall effect of SGLT-2 inhibitors on mean life expectancy was 1.81 years [95% CI: 0.96, 2.73] compared to SOC. Across the whole simulated population, including individuals who never developed any of the three conditions and so were never eligible for treatment, the difference was 0.61 years [95% CI: 0.32, 0.92].

Table 2
Mean difference in cause-specific transition probabilities, age at transition and life expectancy, SGLT-2 inhibitor vs standard of care

Transition	Mean difference in cause-specific transition probabilities (95% CI)	Mean difference in age at transition, years (95% CI)	Mean difference in life expectancy, years (95% CI)
CKD -> CKD-T2DM	-0.012 (-0.027, 0.006)	1.36 (0.47, 2.28)	2.24 (0.84, 3.83)
CKD -> CKD-HF	-0.011 (-0.035, 0.015)	1.36 (0.57, 2.23)	3.76 (1.76, 6.12)
CKD -> Death	0.022 (-0.009, 0.056)	2.36 (0.73, 4.15)	2.36 (0.73, 4.15)
T2DM -> T2DM-CKD	-0.037 (-0.053, -0.020)	0.32 (0.04, 0.61)	2.26 (-0.43, 5.39)
T2DM -> T2DM-HF	-0.011 (-0.023, 0.001)	0.51 (0.06, 1.00)	1.19 (0.32, 2.15)
T2DM -> Death	0.048 (0.028, 0.067)	0.76 (-0.005, 1.65)	0.76 (-0.005, 1.65)
HF -> HF-CKD	-0.034 (-0.100, 0.058)	0.74 (0.23, 1.19)	2.66 (0.99, 4.36)
HF -> HF-T2DM	-0.012 (-0.025, 0.002)	0.69 (0.30, 1.18)	1.40 (0.33, 2.44)
HF -> Death	0.046 (-0.043, 0.111)	1.01 (0.38, 1.75)	1.01 (0.38, 1.75)
CKD-T2DM -> CKD-T2DM-HF	-0.015 (-0.041, 0.017)	1.96 (0.83, 3.22)	2.35 (1.29, 3.62)
CKD-T2DM -> Death	0.015 (-0.017, 0.041)	2.24 (0.79, 3.86)	2.24 (0.79, 3.86)
CKD-HF -> CKD-HF-T2DM	0.005 (-0.018, 0.026)	3.09 (1.42, 4.80)	3.36 (1.84, 5.17)
CKD-HF -> Death	-0.005 (-0.026, 0.018)	3.80 (1.70, 6.27)	3.80 (1.70, 6.27)
T2DM-CKD -> T2DM-CKD-HF	-0.018 (-0.058, 0.026)	1.19 (-0.03, 2.77)	1.71 (0.17, 3.69)
T2DM-CKD -> Death	0.018 (-0.026, 0.058)	2.30 (-0.59, 5.57)	2.30 (-0.59, 5.57)
T2DM-HF -> T2DM-HF-CKD	-0.072 (-0.131, -0.013)	0.99 (0.31, 1.58)	1.35 (0.44, 2.33)
T2DM-HF -> Death	0.072 (0.013, 0.131)	1.38 (0.42, 2.33)	1.38 (0.42, 2.33)
HF-CKD -> HF-CKD-T2DM	0.000 (-0.021, 0.024)	2.04 (0.88, 3.24)	2.38 (1.01, 3.85)
HF-CKD -> Death	0.000 (-0.024, 0.021)	2.68 (0.92, 4.44)	2.68 (0.92, 4.44)
HF-T2DM -> HF-T2DM-CKD	-0.065 (-0.104, -0.008)	1.12 (0.34, 1.78)	1.64 (0.61, 2.61)

CKD: Chronic Kidney Disease; T2DM: Type 2 Diabetes; HF: Heart failure; SOC: Standard of Care; SGLT-2: Sodium Glucose Co-transporter-2 inhibitors; CI: Confidence Interval.

Transition	Mean difference in cause-specific transition probabilities (95% CI)	Mean difference in age at transition, years (95% CI)	Mean difference in life expectancy, years (95% CI)
HF-T2DM -> Death	0.065 (0.008, 0.104)	1.54 (0.51, 2.62)	1.54 (0.51, 2.62)
CKD-T2DM-HF -> Death	0.000 (0.000, 0.000)	2.35 (1.29, 3.62)	2.35 (1.29, 3.62)
CKD-HF-T2DM -> Death	0.000 (0.000, 0.000)	3.36 (1.84, 5.17)	3.36 (1.84, 5.17)
T2DM-CKD-HF -> Death	0.000 (0.000, 0.000)	1.71 (0.17, 3.69)	1.71 (0.17, 3.69)
T2DM-HF-CKD -> Death	0.000 (0.000, 0.000)	1.35 (0.44, 2.33)	1.35 (0.44, 2.33)
HF-CKD-T2DM -> Death	0.000 (0.000, 0.000)	2.38 (1.01, 3.85)	2.38 (1.01, 3.85)
HF-T2DM-CKD -> Death	0.000 (0.000, 0.000)	1.64 (0.61, 2.61)	1.64 (0.61, 2.61)

CKD: Chronic Kidney Disease; T2DM: Type 2 Diabetes; HF: Heart failure; SOC: Standard of Care; SGLT-2: Sodium Glucose Co-transporter-2 inhibitors; CI: Confidence Interval.

For individuals with T2DM as their first condition, SGLT-2 inhibitor treatment was associated with a statistically significant lower probability of progressing to CKD (T2DM-CKD; -0.037 [95% CI: -0.053, -0.020]), a lower but not statistically significant probability of progressing to HF (T2DM-HF; -0.011 [95% CI: -0.023, 0.001]), and a correspondingly higher probability of transitioning directly to death (0.048 [95% CI: 0.028, 0.067]), compared with SOC (Table 2, Fig. 3A). For individuals with T2DM who did not go on to develop a further index condition, mean life expectancy was numerically higher for SGLT-2 inhibitors compared to SOC but not statistically significant (0.76 years [95% CI: -0.005, 1.65]; Table 2).

For individuals with CKD as their first condition, SGLT-2 inhibitor treatment was associated with a lower probability of progressing to CKD followed by T2DM (CKD-T2DM; -0.012 [95% CI: -0.027, 0.006]) and to CKD followed by HF (CKD-HF; -0.011 [95% CI: -0.035, 0.015]), and a correspondingly higher probability of transitioning directly to death (0.022 [95% CI: -0.009, 0.056]), compared with SOC (Table 2, Fig. 3A). However, none of these differences were statistically significant. Mean life expectancy, by contrast, was statistically significantly higher under SGLT-2 inhibitor treatment across all three CKD pathways, including following progression to T2DM (CKD-T2DM; a difference of 2.24 years [95% CI: 0.84, 3.83]).

For individuals with HF as their first condition, SGLT-2 inhibitor treatment was associated with a lower probability of progressing to CKD (HF-CKD; -0.034 [95% CI: -0.100, 0.058]) compared to SOC, and a numerically lower probability of progressing to T2DM (HF-T2DM; -0.012 [95% CI: -0.025, 0.002]; Table 2, Fig. 3A) although neither difference was statistically significant. Mean life expectancy was significantly higher under SGLT-2 inhibitor treatment at both subsequent states (HF-CKD: a difference of 2.66 years [95% CI: 0.99, 4.36]; HF-T2DM: a difference of 1.40 years [95% CI: 0.33, 2.44]).

Across the two-condition states, SGLT-2 inhibitor treatment was associated with a lower probability of progression to the corresponding triple-condition state compared to SOC for five out of the six pathways (Table 2, Fig. 3B), and

two of these differences were statistically significant: progression from T2DM followed by HF to CKD (T2DM-HF to T2DM-HF-CKD: a difference of -0.072 [95% CI: -0.131, -0.013]) and from HF followed by T2DM to CKD (HF-T2DM to HF-T2DM-CKD: -0.065 [95% CI: -0.104, -0.008]). The lack of statistical significance for the remaining pathways reflects the smaller sample sizes and compounded hazard ratio uncertainty of the triple-condition states. Mean life expectancy following direct transition to death from a two-condition state was higher and statistically significant for five of six pathways, ranging from 1.38 years [95% CI: 0.42, 2.33] for T2DM-HF to Death to 3.80 years [95% CI: 1.70, 6.27] for CKD-HF to Death. The exception was T2DM-CKD to Death, where the difference was not statistically significant (2.30 years [95% CI: -0.59, 5.57]) reflecting the increased uncertainty for this transition.

Mean life expectancy following progression to the triple-condition state was consistently statistically higher under SGLT-2 inhibitor treatment (Table 2, Fig. 3C), with differences ranging from 1.35 years [95% CI: 0.44, 2.33] for T2DM-HF-CKD to 3.36 years [95% CI: 1.84, 5.17] for CKD-HF-T2DM.

Mean age at transition also suggests delayed progression to subsequent conditions under SGLT-2 inhibitor treatment. Among individuals with CKD as their first condition, the mean age at transition to T2DM (CKD-T2DM) was significantly older under SGLT-2 inhibitor treatment compared to SOC (74.73 [95%CI: 73.85, 75.72] vs 73.36 [95%CI: 73.24, 73.49] years; difference 1.36 [95% CI: 0.47, 2.28]). A similar, smaller pattern was observed for individuals with HF as their first condition subsequently diagnosed with T2DM (HF-T2DM): 71.88 [95%CI: 71.32, 72.47] vs 71.19 [95%CI: 70.95, 71.38] years (difference 0.69 years [95% CI: 0.30, 1.18]). Among individuals with two pre-existing conditions, the mean age at transition to T2DM as the third condition was higher under SGLT-2 inhibitor treatment, both for those with CKD and HF (CKD-HF to CKD-HF-T2DM: 78.75 [95%CI: 77.01, 80.43] vs 75.65 [95%CI: 75.17, 76.13]; difference 3.09 years [95% CI: 1.42, 4.80]) and for those with HF and CKD (HF-CKD to HF-CKD-T2DM: 76.52 [95%CI: 75.28, 77.80] vs 74.49 [95%CI: 74.08, 74.89]; difference 2.04 years [95% CI: 0.88, 3.24]). These findings indicate that, across all pathways starting with CKD or HF examined, SGLT-2 inhibitor treatment was associated with a delay in the onset of T2DM as a subsequent condition, with the largest delay observed among individuals with both CKD and HF already present (CKD diagnosed first), and the smallest delay among individuals with pre-existing HF alone.

Discussion

We demonstrate that, across a simulated population of 1,000,000 individuals, SGLT-2 inhibitors were modelled to lead to substantial improvements in terms of length of life, with an estimated mean life expectancy gain in individuals with one or more of CKD, T2DM and HF of 1.81 years (95% CI: 0.96, 2.73). Importantly, SGLT-2 inhibitor treatments also consistently delayed the onset of subsequent conditions relative to SOC across all temporal sequences examined. The magnitude of delay varied according to which conditions were already present and their order of onset. Longer life combined with delayed onset of further conditions is consistent with ‘compression of morbidity’, generally regarded as the best possible outcome for preventive treatments.[32] From a population health decision-maker’s perspective, this would represent substantial gains in total life years accrued in the large numbers of people living with one or more of these three conditions.

The inter-connectedness of T2DM, HF, and CKD, described as a cardiorenal-metabolic syndrome, is well established, with each condition increasing the risk of developing the others and accelerating progression once MLTC is present[33]. Observational evidence from linked electronic health records has further demonstrated that the order in which these conditions are acquired has important prognostic implications in a national English cohort of individuals with two of HF, CKD, and T2DM. The order of the first two diagnoses was independently associated with

both the risk of developing the third condition and all-cause mortality, with individuals diagnosed with CKD prior to HF, T2DM prior to CKD, or HF prior to T2DM, each at increased risk of all-cause mortality within disease pairs[34]. Similarly, previous work using the Wales Multimorbidity eCohort and multi-state modelling approach demonstrated that the temporal sequence in which conditions are acquired within a cluster of MLTC can substantially affect life expectancy[35]. Our findings are coherent with this wider literature on the inter-connected, sequence-dependent nature of T2DM, CKD, and HF. The closest modelling studies have projected outcomes of SGLT-2 inhibitors for a single indication or index condition, such as a Markov extrapolation of the DAPA-CKD trial[36] and a UK microsimulation of second-line glucose-lowering therapy in T2DM using routine data[37], in which kidney failure and heart failure hospitalisation were modelled as complications of diabetes over 5 years. By contrast, our framework models the accrual of each condition, in any order, from a population free of all three conditions, and estimates the effect of treatment on life expectancy across all competing pathways.

SGLT-2 inhibitors also differ from many widely used preventive treatments. For example, statins substantially reduce cardiovascular events, but effects on all-cause mortality and disability-free survival are modest or absent, particularly in older people[38]. SGLT-2 inhibitors are one of relatively few treatments, alongside, for example, renin–angiotensin system inhibitors in heart failure with reduced ejection fraction and anticoagulation in atrial fibrillation, with trial evidence of reductions in both disease progression and all-cause mortality, and one of very few with such evidence across several co-existing indications[39,40].

Treatment effects for established interventions have previously been assessed in retrospective pharmacoepidemiological cohort studies[41]. However, there is an increasing need to appraise emerging interventions across MLTC[16]. To our knowledge, this is the first paper to assess the effectiveness of emerging multi-indication treatment options in MLTC populations with competing pathways of disease accrual at a national population-level, which enables representation from under-represented groups such as those from most deprived communities[42]. Whilst the methodology of developing a multi-state model and patient-level simulation is commonly used in HTA[43,44], to our knowledge, it has not previously been used to simultaneously evaluate competing pathways of disease accrual in MLTC and the associated impact on life expectancy.

A limitation of this approach is that clinical trials in single conditions tend to have an under representation of MLTC populations[45], creating potential issues regarding generalisability of treatment effects, particularly to older people and those with comorbidity and frailty. Even when clinical trials include people with MLTC, there is a lack of reporting of treatment effects for these subgroups, which makes them an underused resource in MLTC research[45]. A further limitation is the assumption that treatment effects (hazard ratios) derived from RCT populations translate directly to real-world effectiveness in the simulated MLTC population, which may not hold given differences in adherence, comorbidity burden, and clinical management between trial and routine care settings. In line with the RCTs assuming proportional hazards for treatment and thereby reporting hazard ratios, we further assume that the proportional hazards assumption holds across the lifetime meaning that the hazard ratio remains constant over time and as such the results presented here are likely to reflect an optimistic view of treatment effectiveness. In addition, the natural history model was derived from data collected before widespread use of SGLT-2 inhibitors and glucagon-like peptide-1 receptor agonists; if baseline risks of progression and death are lower in contemporary practice, applying the same relative treatment effects would yield smaller absolute benefits than those estimated here. Parametric models for each transition were selected primarily on statistical fit within a maximum of 13 years of follow-up; although population-scale data reduce reliance on extrapolation, long-term extrapolations were not validated against external data, and alternative models with similar fit could produce different lifetime estimates[46].

Finally, transition hazards depended on the current health state (including the order in which conditions were diagnosed), age, sex and deprivation, but unmeasured individual-level factors that jointly influence several transitions, such as frailty, were not modelled.

Furthermore, in this research, we included all individuals with HF following methodology by Kuan, et al. [47]. However, SGLT-2 inhibitors are currently recommended by NICE in a targeted population including chronic HF with reduced ejection fraction or preserved and mildly reduced ejection fraction. At the time of this study, ICD-10 codes did not differentiate between HF with reduced and preserved ejection fraction, with the ICD-10 code, I50.33, for HF with reduced ejection fraction only becoming effective on 1 Oct 2021. With more granular levels of clinical coding becoming increasingly available, future studies may allow assessment of targeted and optimised populations, provided that sufficiently granular codes are used in routine clinical practice.

Decision-makers such as NICE typically appraise treatments separately for each indication. Where a treatment affects several conditions that commonly co-exist, and people may develop more than one of them over time, appraising each indication in isolation ignores effects on subsequent disease and survival that could change recommendations. Modelling the overall impact of a multi-indication therapy across all relevant conditions over a lifetime horizon, as demonstrated here, provides a more complete basis for decision-making. In this case study, SGLT-2 inhibitors increased life expectancy and delayed diagnosis of further conditions across most pathways, although the size of the benefit varied with the order in which conditions developed and was not statistically significant for all pathways.

Although all hazard ratios for SGLT-2 inhibitors used in this simulation were below 1, indicating a reduction in the instantaneous risk of every transition, total life years did not increase for all transitions. For example, a higher proportion of individuals with T2DM moved directly to the death state (Fig. 3A), with no statistically significant difference in life expectancy (a difference of 0.76 years [95% CI: -0.005, 1.65]) under SGLT-2 treatment compared to SOC. This finding of reduced morbidity (fewer diagnoses of CKD and heart failure in people with T2DM) without statistically significant improved life expectancy illustrates an important feature of competing-risks multi-state models in that uniformly reducing cause-specific hazards does not guarantee a uniform improvement in downstream outcomes. This is because the relative magnitude of hazard reductions across competing transitions determines which transition an individual experiences next. In other words, because SGLT-2 inhibitors delay progression to CKD and HF more than they delay death, more people with T2DM die before a further condition is diagnosed, even though treatment does not increase anyone's risk of death.

This underscores the importance of evaluating multi-indication therapies such as SGLT-2 inhibitors using a whole-pathway, patient-level simulation approach rather than relying on transition- or condition-specific treatment effects alone, particularly in populations with MLTC where the sequence and combination of conditions substantially influences prognosis. It also highlights a broader methodological point for the evaluation of treatments in MLTC, in that favourable effects on individual disease-specific outcomes (such as delayed time to death in isolation) cannot be assumed to translate into proportionate gains in observed life expectancy at the population level, because the benefit realised depends on how treatment redistributes individuals across competing pathways.

From our work with patients and public involvement and engagement groups, many individuals living with MLTC expressed a clear preference to prioritise quality of life over quantity of life in healthcare decision-making, which is further supported by the literature[48]. Thus, an intervention that delays progression of disease, or accumulation of further disease, without meaningfully increasing life expectancy (as we see in the T2DM only, and T2DM followed

by CKD (T2DM-CKD) pathways) is likely of considerable value to most patients, and extending life *and* delaying morbidity is likely of even more value. A holistic approach that evaluates interventions (treatments and lifestyle changes) across MLTC is therefore crucial to appropriately inform patients and carers to enable informed patient and carer choice.

In this paper we present a modelling framework that combines estimates of treatment effects from RCTs with estimates of transition hazards obtained from population-scale data to create synthetic datasets to model multi-indication therapies in people living with one or more of T2DM, CKD, and HF. This framework could be applied to any situation involving the appraisal of emerging interventions in multiple, commonly co-existing conditions, for example drug repurposing or repositioning in Alzheimer's disease dementia[49], and cancer[50]. However, this framework could also be extended to include the assessment of a sequence of multiple treatment options used in disease-specific management in MLTC, and where applicable, the comparison of a sequence of treatments with multi-indication therapies. The framework could also be applied beyond MLTC, for example to treatments such as antihypertensives that may have both direct effects on outcomes and indirect effects mediated through intermediate events or subsequent conditions[51]. The framework could also be applied to evaluate the effect of interventions for a specific target population defined by the simulated covariate values used in the transition-specific regression models.

Future research could build on this work to include validation of the modelling framework against individuals receiving SGLT-2 inhibitors in routine practice. Furthermore, as people with MLTC are under-represented in many RCTs[45], routinely collected data could be used to calibrate or transport trial-derived hazard ratios to populations with MLTC. This approach was not possible using the WMC owing to limited follow-up following the approval of SGLT-2 inhibitors in this population (maximum of 5 years in T2DM, and no data for CKD and HF). Further work could build on this framework to assess cost-effectiveness of emerging interventions in populations with MLTC. Alongside quantity of life, evaluation of quality of life is an important consideration in cost-effectiveness analyses but would require adequate reporting of quality of life measures by disease combinations in clinical trials and/or observational studies. With increasing numbers of trials in MLTC populations reporting on alternative outcomes of importance to patients, clinicians, and healthcare decision-makers, such as independent living and quality of life measures[52], thorough assessment of cost-effectiveness in populations with MLTC will become increasingly feasible.

SGLT-2 inhibitors have a marketing authorisation for treating, but not preventing or delaying, T2DM, CKD and HF. Future research could include RCTs or target trial emulations using routinely collected data evaluating the relative merit of SGLT-2 inhibitors in preventing or delaying disease progression. Our health states were defined by the first recorded diagnosis of each condition and did not distinguish disease severity, such as CKD stage, HF symptom class or duration of diabetes. The benefits of slowing disease progression may be greatest for people diagnosed earlier, with mild or moderate disease, who have the longest time over which to accrue benefit. Future studies incorporating measures of severity, such as eGFR, albuminuria or HbA1c from linked laboratory data, could assess whether the effects of SGLT-2 inhibitors differ by disease stage at treatment initiation. Studies with longer follow-up would also be valuable, and some of the benefits of delayed progression may only become apparent over longer periods.

This work demonstrates that understanding multi-indication therapies in MLTC requires looking beyond single conditions and single endpoints or transitions to the whole disease pathway. Multi-state models applied to population-scale linked health data, combined with patient-level simulation, provide a flexible framework to assess

the effect of interventions in MLTC populations. Such an approach provides a holistic perspective on the prevention and management of MLTC that accounts for when, and in what order, conditions develop over the life course.

Methods

Study design

This study adopts a Health Technology Assessment (HTA) approach, combining a natural history model derived from real-world, population health data, routinely collected in the period prior to widespread use of SGLT-2 inhibitors, with treatment effect estimates of SGLT-2 inhibitors derived from randomised controlled trials (RCTs). This approach enables estimation of the anticipated population-level impact of SGLT-2 inhibitors as multi-indication therapies for individuals with MLTC. More generally, our work provides a method for evaluating the potential clinical effectiveness of emerging treatments and their associated synergistic or sub-additive effects on patient outcomes across MLTC on a population scale, before there are sufficient real-world data available to estimate these effects directly from routine data.

We conducted a population-scale retrospective cohort study using the Wales Multimorbidity e-Cohort (WMC) held within the Secure Anonymised Information Linkage (SAIL) Databank.[53] The SAIL Databank Independent Information Governance Review Panel (IGRP) approved this research (SAIL Project: 1744) and the development of the WMC[54]. Estimated treatment effects and associated uncertainty were obtained from published RCTs. Clinical trial number: not applicable, as this is an observational and modelling study using routinely collected, anonymised data; treatment effects were taken from published randomised controlled trials.

Data sources and setting

The WMC has linked demographic, mortality, and electronic health record (EHR) data, using anonymised linkage fields at the individual-participant level from 1st January 2000 to 31st December 2019. Records were linked across datasets with an anonymised linking field assigned by a trusted third party using deterministic and probabilistic matching of identifiable fields[55]. Record linkage for the SAIL Databank is carried out by a trusted third party (Digital Health and Care Wales, formerly the NHS Wales Informatics Service) using a split-file process: identifiable fields (NHS number, name, date of birth, sex and postcode) are matched by deterministic and then probabilistic methods, and each individual is assigned an anonymised linking field (ALF) before the de-identified clinical content is transferred to SAIL. The ALF was used to link all datasets in this study. The linkage methods and their accuracy are reported by Lyons et al.[55] and Ford et al.[53]. The authors had access to the complete linked, de-identified WMC population within the SAIL Databank TRE. Demographic data, including administrative information for the population of Wales registered to a General Practice, were obtained from the Welsh Demographic Service Dataset (WDSD). Mortality data, including information regarding the dates and cause of death for all Welsh residents (including those who died outside of Wales), were obtained from the Annual District Death Extract (ADDE) from the Office for National Statistics (ONS). EHR data were obtained for individuals registered to a SAIL providing General Practice. Diagnoses and dates of diagnoses were obtained from the Welsh Longitudinal General Practice (WLGP) data and Patient Episode Database for Wales (PEDW). International Classification of Diseases, Tenth Revision (ICD-10) codes were used to capture inpatient diagnoses from PEDW, and Read codes were used to capture primary care recorded diagnoses from WLGP. For individuals with multiple diagnosis dates for the same condition, the first recorded diagnosis date was used. Full information regarding curation of the data in WMC and associated methodology can be found in Lyons, *et al*.[54]

Participants

The WMC is a population-based cohort of all individuals living in Wales, developed to investigate the accrual of multiple long-term conditions; it therefore includes individuals with and without MLTC[54]. We included all individuals aged 25 years and over, alive and living in Wales on 1st January 2000 with follow-up until 31st December 2012 (prior to the first NICE recommendation on the use of SGLT-2 inhibitors in T2DM, HF and CKD), first Welsh residency break (identified from the WDSD), or death. Individuals had a minimum of one day and a maximum of 13 years of follow-up. We restricted the population to individuals registered with a General Practice providing data to the SAIL Databank to ensure that all EHR data, including all primary care data, were captured. Analysis includes 1,311,822 individuals, covering approximately 86% of the whole population of Wales across all health boards providing primary care data to the SAIL Databank. A 2-year clearance period (i.e., a period during which recorded diagnoses were assumed to reflect prevalent rather than incident disease) of T2DM, HF and CKD was applied to ensure only new diagnoses were captured, where prior work has demonstrated the robustness of MLTC diagnoses in this population to varying levels of clearance periods from 1 to 10 years[31]. Due to very small numbers (n = 11) of individuals diagnosed with two or more conditions on the same date, same day diagnoses were excluded from the analysis because transitions estimated from such small numbers could not be released from the TRE without risk of disclosure. The derivation of the study cohort is shown in Supplementary Fig. 1. There were no missing data on age, sex or deprivation quintile in the analysed cohort (Table 1).

Outcome measures

The primary outcome measure was estimated mean life expectancy identified using the ADDE death records and transition rates to death. Secondary outcome measures included transition rates and cause-specific transition probabilities between health states for T2DM, HF, and CKD. Health states were defined as the first diagnosis of T2DM, HF, CKD, or their combinations based on Read codes (version 2) obtained from WLGP and ICD-10 codes obtained from PEDW. Read codes and ICD-10 codes for T2DM,[56,57] HF,[47] and CKD[58,59] were obtained from established code lists, curated and evaluated for UK primary care and hospital records, and are provided in Supplementary Table 2.

Statistical Analysis

Natural History of Disease Model

Markov multi-state models were used to model trajectories of disease in T2DM, HF, and CKD and their associated impact on mortality[35]. Figure 1 illustrates the multi-state model that was used to model trajectories of disease for combinations of T2DM, HF, and CKD. At cohort inception, all individuals start in the index health state of not having any of the three conditions. The solid lines indicate that individuals can transition to death or other health states, with death included as an absorbing state in the model. A multi-state model simultaneously estimates each disease pathway via modelling of all possible transitions between health states. Time to diagnosis or time to death in years was used as the timescale. Each transition was modelled with its own baseline hazard and covariate effects (i.e., no parameters were shared across transitions); dependence between transitions arises through the state structure, in which each health state is defined by the conditions present and the order in which they were diagnosed. Individuals were censored on the first date of a break in Welsh residency, cohort end (31st December 2012), or date of death where death is treated as a competing risk. Parametric survival models were fitted

(exponential, Weibull, gamma, Gompertz, log-normal, log-logistic, and generalised gamma), adjusted for age at entry into the health state using a time-varying covariate, sex, and Welsh Index of Multiple Deprivation (WIMD) with men in the 3rd WIMD quintile (middle deprivation) as the reference. Parametric survival models were selected as they are commonly used to extrapolate beyond the observation window, and for this reason are frequently preferred in health technology assessments[46]. Statistical fit was assessed using AIC, BIC (Supplementary Table 3) and visual fit of the survival (Supplementary Fig. 2) and hazard curves (Supplementary Fig. 3). The best fitting parametric model was selected for each transition (Supplementary Table 4).

Patient-level simulation

Parameter estimates of the parametric survival models for each transition were obtained from the multi-state model with the best statistical fit and used to simulate a SOC population. A simulated population of 1,000,000 individuals was generated to obtain stable estimates of transition probabilities and life expectancy across all disease states, including the less-populated MLTC states. Age at baseline was drawn from a normal distribution with a mean of 60 years and standard deviation of seven years (reflecting the average age of the population at the first index diagnosis from the natural history of disease model), and centred at 65 years (average age in RCTs of SGLT-2 inhibitors) for use in regression models. Sex was assigned by sampling from a Bernoulli distribution with equal probability ($p = 0.5$), yielding an approximately equal split of men and women. Deprivation was assigned using the Welsh Index of Multiple Deprivation (WIMD), categorised into five quintiles ranging from least to most deprived. Each quintile was assigned with equal probability (0.20), reflecting the construction of WIMD quintiles, each of which contains 20% of small areas in Wales, and consistent with the observed cohort distribution (18–21% per quintile; Table 1). A random seed was set prior to simulation to ensure reproducibility. Hazard ratios (HR) and associated uncertainty for SGLT-2 inhibitors for each transition were obtained from a targeted literature review to identify eligible trials; full details are provided in Supplementary Fig. 4 and Supplementary Tables 5 and 6. Hazard ratios were applied via a proportional-hazards transformation of the survival curve obtained from the simulated SOC population, with each individual mapped to their own percentile of that curve, preserving within-person correlation across competing events and between treatment arms (i.e., common random numbers[43]). For participants who have all three conditions simultaneously (T2DM, HF and CKD in different temporal ordered sequences), hazard ratios were not reported for time to death for dapagliflozin. As such the most conservative hazard ratio (HR: 0.91, 95%CI: 0.67, 1.25) of dual conditions was used (Supplementary Tables 6 & 7).

To capture uncertainty in the estimated treatment effects, a Monte Carlo simulation approach was used across 100 iterations. The number of iterations was chosen to balance computational burden (1,000,000 individuals simulated per arm at every iteration) against Monte Carlo error; the stability of the estimated means and of the 2.5th and 97.5th percentiles was assessed using running-quantile trace plots and Monte Carlo standard errors (bootstrap for the percentiles) (Supplementary Figs. 5 and 6). At each iteration, treatment effect parameters were sampled independently from normal distributions on the log hazard ratio scale defined by the point estimates and standard errors reported in the published RCT literature (Supplementary Table 7). Baseline characteristics of the simulated population were generated once; at each iteration, treatment effects were resampled and event times were redrawn, so that both parameter uncertainty and stochastic variability were reflected in the final estimates. Uncertainty intervals were derived as the 2.5th and 97.5th percentiles of the distribution of life expectancy estimates across the 100 iterations. Estimated mean life expectancy and associated uncertainty was calculated for different temporally ordered sequences of MLTC and compared for SGLT-2 inhibitor and SOC treated populations. For each health state, the transition probability represents the proportion of individuals entering that state who next transition to each of the available competing states (including death), estimated empirically from

the simulated cohort. All analyses were performed using R version 4.5.0 and the natural history of disease model was fitted in the SAIL Databank Trusted Research Environment (TRE)[53,55]. The patient-level simulation code is available at https://github.com/r-k-owen/REMIT.

Patient and Public Involvement

The Re-thinking Health Policy in Multiple Long-Term Conditions (REMIT) project[60] has a dedicated patient and public involvement and engagement group, including a representative panel from across the UK living with MLTC. The panel specifically discussed and directly fed into this work, including the research design, interpretation of the findings, and dissemination. A public contributor also reviewed a draft of this manuscript and provided feedback on the clarity, accessibility and relevance of the findings, which was incorporated into the final version. Furthermore, we worked with the SAIL Consumer Panel and the independent Information Governance Review Panel (IGRP) that includes members of the public to develop the WMC[54], and study design, protocol and findings from this work (IGRP Projects: 0911 and 1744).

Declarations

Competing interests

RKO is a Health and Care Research Wales (HCRW) Senior Research Leader (SRL-25-019), member of the National Institute for Health and Care Excellence (NICE) Technology Appraisal Committee, member of the NICE Decision Support Unit (DSU), and associate member of the NICE Technical Support Unit (TSU). She has served as a paid consultant to the pharmaceutical industry, providing unrelated methodological advice. She reports teaching fees from the Association of British Pharmaceutical Industry (ABPI) and the University of Bristol.

Author contributions

Conceptualisation of the study: RKO; Data curation: RKO, IH, JL, RAL; Analysis: RKO; Drafting of the paper: RKO; Review, editing and final approval of the manuscript: All authors; Funding acquisition: RKO.

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Data availability statement

Data from the patient level simulation can be reproduced using the code provided at https://github.com/r-k-owen/REMIT. Access to the data used for the natural history of disease model are available to the research community upon approval by the SAIL Databank (https://saildatabank.com/data/apply-to-work-with-the-data/). All proposals to use data held within the SAIL Databank are subject to review and approval by an independent Information Governance Review Panel (IGRP).

Code availability

The patient-level simulation code is available at https://github.com/r-k-owen/REMIT.

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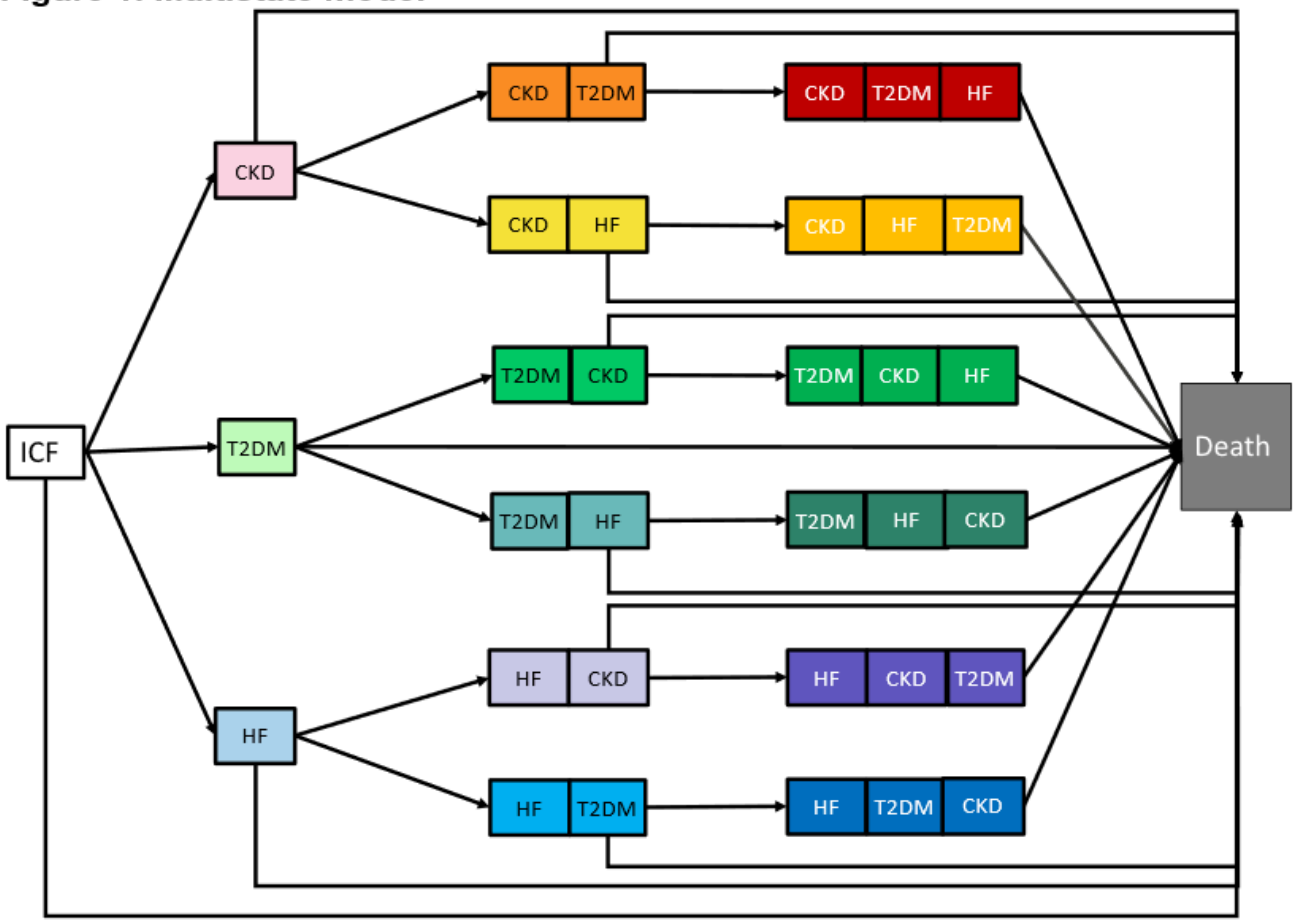
Figures

Figure 1: Multistate model

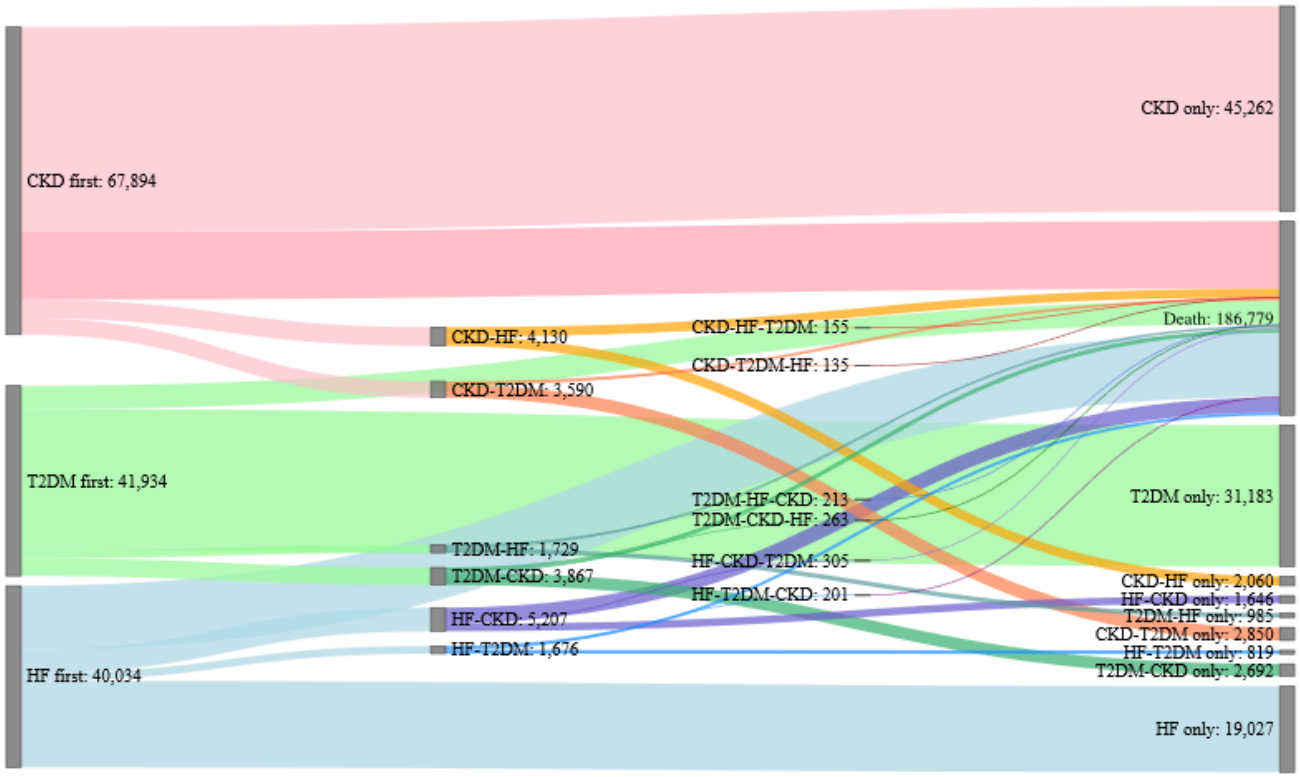


ICF: Index condition free; CKD: Chronic Kidney Disease; T2DM: Type 2 Diabetes; HF: Heart failure

Figure 1

See image above for figure legend

Figure 2: Sankey flow diagram from natural history of disease model



CKD: Chronic Kidney Disease; T2DM: Type 2 Diabetes; HF: Heart failure

Figure 2

See image above for figure legend

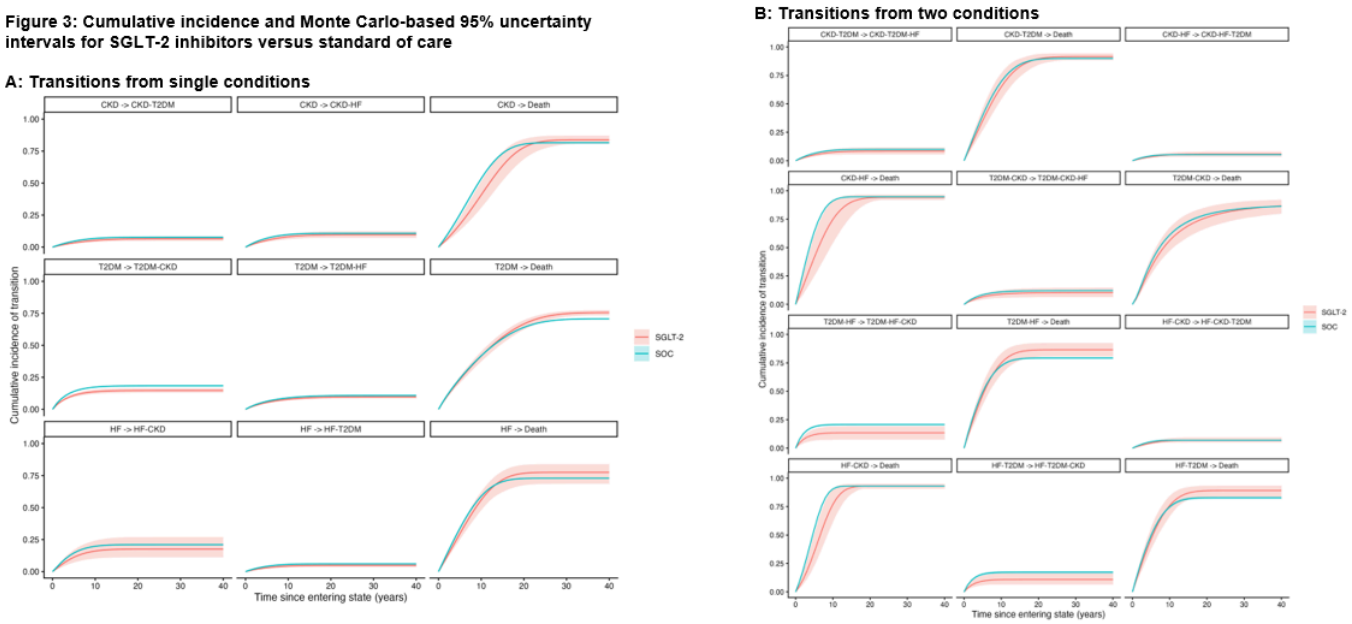


Figure 3

See image above for figure legend

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