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Expected Health Benefits of SGLT-2 Inhibitors and GLP-1 Receptor Agonists in Older Adults

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Abstract

Background. Older and sicker adults with type 2 diabetes (T2D) were underrepresented in randomized trials of glucagon-like peptide 1 receptor-agonist (GLP1RA) and sodium-glucose cotransporter 2 inhibitors (SGLT2I), and thus, health benefits are uncertain in this population. **Objective.** To assess the impact of age, health status, and life expectancy in older adults with T2D on health benefits of GLP1RA and SGLT2I. **Design.** We used the United Kingdom Prospective Diabetes Study (UKPDS) model to simulate lifetime health outcomes. We calibrated the UKPDS model to improve mortality prediction in older adults using a common geriatric prognostic index. **Participants.** National Health and Nutrition Examination Survey 2013–2018 participants 65 y and older with T2D, eligible for GLP1RA or SGLT2I according to American Diabetes Association guidelines. **Interventions.** GLP1RA or SGLT2I use versus no additional medication. **Main Measures.** Lifetime complications and weighted life-years (LYs) and quality-adjusted life-years (QALYs) across overall treatment arms and life expectancies. **Key Results.** The overall older adult population was predicted to experience significant health benefits from GLP1RA (+0.29 LY [95% confidence interval: 0.27, 0.31], +0.15 QALYs [0.14, 0.16]) and SGLT2I (+0.26 LY [0.24, 0.28], +0.13 QALYs [0.12, 0.14]) as compared with no added medication. However, expected benefits declined in subgroups with shorter life expectancies. Participants with <4 y of life expectancy had minimal gains of <0.05 LY and <0.03 QALYs from added medication. Accounting for injection-related disutility, GLP1RA use reduced QALYs (−0.03 QALYs [−0.04, −0.02]). **Conclusions.** While GLP1RA and SGLT2I have substantial health benefits for many older adults with type 2 diabetes, benefits are not clinically significant in patients with <4 y of life expectancy. Life expectancy and patient preferences are important considerations when prescribing newer diabetes medications.

Highlights

- On average, older adults benefit significantly from SGLT2I and GLP1RA use. However, the benefits of these drugs are not clinically significant among older patients with life expectancy less than 4 y.
- There is potential harm in injectable GLP1RA use in the oldest categories of adults with type 2 diabetes.
- Heterogeneity in life expectancy and patient preferences for injectable versus oral medications are important to consider when prescribing newer diabetes medications

Keywords
type 2 Diabetes, older adults, simulation modeling SGLT-2 inhibitors, GLP-1 receptor agonists

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Introduction

Type 2 diabetes (T2D) in older adults (≥65 y of age) is a significant and growing public health challenge. Among older adults, the prevalence of diagnosed diabetes has been steadily rising from 13.2% in 1997 to 21.4% in 2018.[1,2] Across age groups, older adults with T2D have the highest risk of microvascular and cardiovascular (CV) complications, hypoglycemia, and mortality.[1–4] Given the growing burden of diabetes, it is important to identify treatments that minimize the risk of complications.

Glucagon-like peptide 1 receptor-agonist (GLP1RA) and sodium-glucose cotransporter 2 inhibitors (SGLT2I) are 2 new classes of diabetes medications that have been found in cardiovascular outcome trials (CVOTs) to produce CV and renal benefits in selected populations of adults with T2D.[5–15] Accordingly, the American Diabetes Association (ADA) has recommended that adults with atherosclerotic cardiovascular disease (ASCVD) or at high risk for ASCVD, chronic kidney disease (CKD), or congestive heart failure (CHF), consider incorporating GLP1RA or SGLT2I with demonstrated CV benefit into diabetes treatment.[16]

While these newer agents hold great promise, it is unclear how they will affect the health of older and sicker patients not well represented in randomized trials. While CVOT populations included a significant proportion of adults age ≥ 65 y, representation among adults age ≥ 75 y was much lower (range: 6.3%–11%).[17] In addition, older adults with significant comorbidities, functional impairments, or limited life expectancy were specifically excluded from CVOT.[18] These important patient characteristics have previously been shown to diminish the benefits of intensive glucose control and thus must be considered when assessing the health benefits of newer diabetes agents.[19] In addition, the risk of medication adverse events is also important when deciding to initiate these agents in older adults.[20,21]

One approach to studying how patient heterogeneity influences the clinical effects of a given therapy is to integrate existing insights from geriatrics, natural history of disease, and treatment effects via disease simulation modeling. Without directly available randomized trial data regarding treatment effects for specific patient subgroups, providers and patients must implicitly integrate trial findings with the clinical context of the individual patient. Disease simulation modeling can be used to formally estimate the treatment effect and associated uncertainty for these understudied subpopulations. This is informative for both patients and providers as well as clinical guideline developers making recommendations regarding the optimal clinical scenarios for prescribing newer diabetes treatments. In this study, we use disease simulation modeling to evaluate how the lifetime health benefit of GLP1RA or SGLT2I versus no medication varies for older patients with T2D across age and health status.

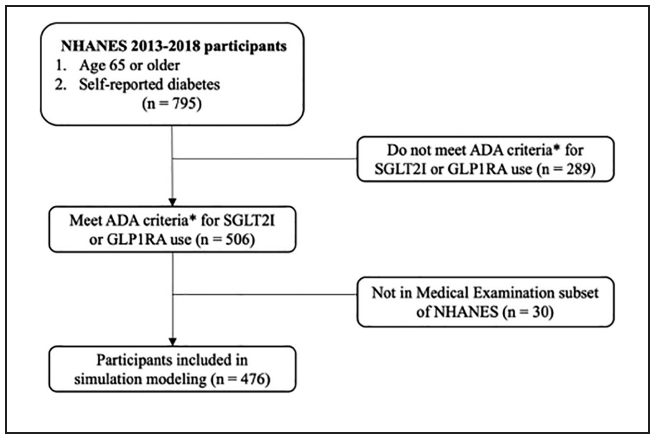

Figure 1 NHANES 2013–2018 participants included in simulation modeling.
*ADA criteria for SGLT2I or GLP1RA use include adults with current atherosclerotic cardiovascular disease (ASCVD), who are at high risk for developing ASCVD, or who have heart failure or chronic kidney disease (CKD) to be placed on either a SGLT2I or GLP1RA. ADA, American Diabetes Association; GLP1RA, glucagon-like peptide-1 receptor agonist; NHANES, National Health and Nutrition Examination Survey; SGLT2I, sodium-glucose cotransporter-2 inhibitor.

Methods

Study Population

We identified a sample of US adults age ≥ 65 y with self-reported T2D from the National Health and Nutrition Examination Survey (NHANES) 2013–2018 (Figure 1). The sample included those not currently taking but eligible for treatment with SGLT2I or GLP1RA according to 2021 ADA guidelines (see eMethods "Study Population").[16]

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Model Inputs

Individual patient-level data from NHANES were used for baseline input in the simulation model (Table 1). Details about model inputs and imputation of missing participant characteristics are provided in the supplemental material (see eTables 1 and 2, eMethods "Model Inputs and Missing Variables").

To characterize heterogeneity in health and functional status across the study population, we utilized a widely used model of mortality in older adults developed by Lee et al. (referred to as the Lee index) to calculate a mortality risk score for NHANES participants.[22,23] The Lee index was originally developed for 4-year mortality and validated in a sample of the US-based Health and Retirement Study, in which there was a 16% prevalence of diabetes.[22] It has also been shown to accurately predict 10-y mortality risk and has undergone external validation.[24,25] We obtained the original regression coefficients of the 4-y prognostic index from the developers (eTable 3).

Risk factors included in the 12-item Lee index include age, sex, diabetes, cancer, lung disease, heart failure, body mass index < 25 kg/m^2, current smoker, and difficulty with functional measures including bathing, managing finances, walking several blocks, and pushing/pulling heavy objects. Each risk factor included in the Lee index is associated with a point value, with higher point values correlating with increased risk of mortality (eTable 3). All variables were available in NHANES, which allowed us to calculate mortality risk according to the Lee index score for model participants. Due to the limited size of the NHANES sample, participants were stratified into discrete categories associated with Lee index scores (1–4 points, 5–9 points, 10–14 points, 15+ points) and age (65–74 y, 75+ y; see eTable 4, eMethods "Lee Index").

Table 1. NHANES 2013–2018 Participant Inputs for Simulation Modeling

Characteristic	Mean[a] (*s*) or Proportion
Age	73.31 (5.27)
Lee index points, mean	8.83 (3.07)
Lee index points, population proportion	
1–4, %	5.46
5–9, %	48.74
10–14, %	37.18
15+, %	8.61
Medications, proportion use	
Metformin, %	78
Sulfonylurea, %	47
Thiazolidinedione, %	5
Dipeptidyl peptidase-4 inhibitor, %	17
Meglitinide, %	0.2
α-Glucosidase inhibitor, %	0.8
Insulin, basal, %	2
Insulin, short-acting bolus, %	2
Insulin, medium-acting bolus, %	0.7
Female	39.06
Black/African American	22.09
Current smoker	15.54
Diabetes duration	14.83 (10.97)
CHF history	16.77
Stroke history	16.36
MI history	19.63
ESRD history	1.02
Heart rate, beats/min	70.38 (11.56)
Systolic blood pressure, mm Hg	140.86 (21.26)
Body mass index, kg/m^2	30.56 (6.41)
HbA1c level, %	6.87 (1.15)
Estimated glomerular filtration rate, mL/min/1.73 m^2	68.42 (23.33)
Low-density lipoprotein cholesterol level, mmol/L	2.26 (0.83)
High-density lipoprotein cholesterol level, mmol/L	1.25 (.38)
Hemoglobin level, g/dL	13.39 (1.67)
White blood cell count, 1,000 cells/μL	7.37 (1.96)
Albuminuria	35.92

CHF, congestive heart failure; ESRD, end-stage renal disease; HbA1c, glycated hemoglobin; MI, myocardial infarction; NHANES, National Health and Nutrition Examination Survey.

[a]Multiple imputation was performed for model inputs that were missing for some NHANES participants, including heart rate, systolic blood pressure, body mass index, HbA1c, estimated glomerular filtration rate, low-density and high-density lipoprotein cholesterol, hemoglobin, and white blood cell count.

Simulation Model

We adapted an individual patient-level, Monte Carlo–based Markov simulation model of the complications and mortality related to T2D based on risk equations from the United Kingdom Prospective Diabetes Study Outcomes Model version 2 (UKPDS OM2; eFigure 1).[26] The model uses 26 patient-level characteristics and 13 risk equations to predict lifetime risk for diabetes-related complications. UKPDS includes 4 separate mortality equations and in any patient-year, only 1 of the 4 mutually exclusive mortality equations is used, depending on health history and complications (eTable 5; see eMethods "Simulation Model Structure").

The UKPDS allows for mortality predictions that incorporate the complex and dynamic interplay between individual characteristics, biomarkers, and complications associated with T2D. However, the original UKPDS

study excluded individuals 65 y and older and those with severe illness that might "limit life or require extensive systemic treatment."[27] To account for the impact of advanced age and complex functional status in older adults with diabetes, we calibrated the risk intercept of all 4 UKPDS mortality equations by using mortality estimates from the Lee index as a gold standard (eTable 5).[22,25] In our calibration, we preserved the UKPDS mortality equation structure while incorporating the knowledge present in the Lee index. This allowed us to stratify model participants at varying risk for mortality, represented by discrete categories of Lee index points (1–4, 5–9, 10–14, 15+). Subsequently, we were able to examine the interplay between life expectancy and health benefits from GLP1RA and SGLT2I. Our model calibration methods are based on those established during the Ninth Mount Hood Diabetes Challenge[28] (see eMethods "Calibration of UKPDS OM2 Mortality Equation").

Estimating Treatment Benefit

We compared the initiation of GLP1RA or SGLT2I versus no additional medication. The 2 main approaches used by prior studies to estimate the effect of newer diabetes drugs have been modeling via either risk factor reduction (e.g., HbA1c, low-density lipoprotein, weight etc.)[29,30] or reduction in health event probabilities (e.g., myocardial infarction [MI], stroke).[31,32] Prior work has demonstrated that the health effects of GLP1RA or SGLT2I are not fully captured by reductions in risk factors.[33,34] Thus, we chose to model the direct reduction in health event probabilities for the base-case analysis, to allow for a maximum estimate of drug benefit. We assume a constant annual treatment effect with medication use. We model reductions in risk factors in sensitivity analysis (see eMethods "Modeling Drug Effect").

We obtained estimates for health event and risk factor reductions and rate of adverse events for GLP1RA and SGLT2I from 2 recently published meta-analyses examining the longer-term effects (52 wk) of these drugs[35,36] (eTable 6). Using published details from the meta-analyses, we calculated estimates for annual reduction in health event probability and 1-time risk reduction in risk factors (see eMethods "Calculating Health Outcome and Risk Factor Reductions from Meta-Analyses"). Adverse events included gastrointestinal complications for GLP1RA and diabetic ketoacidosis and genital infections for SGLT2I. If an individual experienced a medication adverse event, they would discontinue the medication and, accordingly, not experience a reduction in health event probabilities for the remaining model cycles.

For the "no additional medication" arm, the risk of future events was based solely on incorporating the clinical characteristics of NHANES participants into UKPDS OM2 risk equations. Because of the time period (1980s–1990s) during which the UKPDS was conducted, these risk equations essentially account for any ancillary effects of older diabetes medications (i.e., metformin, insulin, sulfonylureas). The rate of medication use in the original UKPDS cohort is previously reported.[37]

Health Utilities

To calculate quality-adjusted life-years (QALYs), we used established utilities that accounted for the independent effects of each of the diabetes-related complications, medication adverse events, and injection medication use (eTable 7). QALYs were calculated using the multiplicative method, which entails multiplying all utility values within a patient cycle. Health utilities were discounted at 3% annually.

Base-Case Analysis

We compared the lifetime complication rates and NHANES-weighted life-years (LYs) and QALYs associated with GLP1RA and SGLT2I treatment compared with no additional medication. We report outcomes across discrete health status categories associated with Lee index scores (1–4 points, 5–9 points, 10–14 points, 15+ points) and age (65–74 y, 75+ y). Base-case results incorporate NHANES mobile examination center (MEC) weights to provide estimates of drug effectiveness in the US older adult population. Each NHANES participant underwent 5,000 simulations (each simulation representing a patient life) for no additional medication, GLP1RA, and SGLT2I treatment arms (see eMethods "Calculation of Incremental Outcomes and Confidence Intervals"). Models were run using R 4.0.4. Descriptive analyses were conducted using SAS version 9.4.

Sensitivity Analyses

We conducted several 1-way sensitivity analyses. First, we performed a sensitivity analysis demonstrating average outcomes that do not incorporate NHANES weights. Second, given that the majority GLP1RA are injectable drugs, we evaluated the impact of injection-related disutility on QALYs for the GLP1RA arm. Third, we modeled the drug benefits of GLP1RA and SGLT2I via reduction in risk factors as opposed to reductions in health event probabilities (see eMethods "Modeling Drug Effect"). Fourth, we evaluated the uncertainty in using mean estimates for reduction in

Table 2 Lifetime Percentage Prevalence of Diabetes Complications by Treatment Arm

	Initial Prevalence	No Additional Medication	GLP1RA	SGLT2I
Macrovascular outcomes				
CHF	17.2	27.2	27.4	25.0
IHD	27.5	36.6	36.9	36.7
MI	20.1	34.8	35.1	34.1
Stroke	16.8	28.4	27.6	28.7
Microvascular outcomes				
Amputation	0	4.4	4.5	4.5
Blindness	0	5.2	5.3	5.2
Ulcer	0	2.4	2.5	2.5
ESRD	1.1	4.7	4.1	4.7
Adverse events				
GI complications	0	0	27.4	0
DKA	0	0	0	0.4
Genital Infection	0	0	0	23.2

CHF, congestive heart failure; DKA, diabetic ketoacidosis; ESRD, end-stage renal disease; GI, gastrointestinal; GLP1RA, glucagon-like peptide 1 receptor agonist; IHD, ischemic heart disease; MI, myocardial infarction; SGLT2I, sodium-glucose cotransporter 2 inhibitor.

health event probabilities by conducting a worst-case and best-case scenario analysis for GLP1RA and SGLT2I, based on the upper and lower end of the 95% confidence interval (CI) estimates (eTable 6). The 95% CI estimates from the Alexander et al. meta-analysis are relatively narrow, however, given the large number of trials included in the analysis. Because our target population of older adults was often excluded from trials used in the meta-analysis, there is a concern that we might not have captured the true treatment effect of GLP1RA and SGLT2I in our understudied population. Accordingly, we reduced the treatment effect by 75% and 90% to assess if there remains a clinically meaningful quality-of-life effect under these alternative assumptions. Next, the NHANES population had a relatively low glycated hemoglobin level (mean: 6.87) compared with that of the CVOT populations. Thus, we modeled the impact of a higher baseline HbA1c of 8.0% on incremental outcomes for treatment arms. Next, given that semaglutide is the sole oral GLP1RA approved in the United States, we conducted an evaluation of oral semaglutide using data from the PIONEER 6 trial (see eMethods "Oral Semaglutide").[14] Finally, we investigated the impact of the new drugs in the broader population of older adults with T2D, regardless of ADA eligibility criteria.

Results

Population

There were 476 participants in NHANES 2013–2018, representing 4.86 million US adults ages 65 y and older with T2D and eligible for treatment with GLP1RA or SGLT2I (Table 1). The average age was 73 y. The average Lee index score was 9 points. Approximately 5% of participants had Lee index scores of 0 to 4 points, 49% with 5 to 9 points, 37% with 10 to 14 points, and 9% with 15+ points (see eTable 4 for further descriptive differences across 7 major health status categories).

Simulation Model Performance

We compared life expectancy estimates for the drug-eligible older adult population with T2D in NHANES 2013–2018 using the original and calibrated UKPDS OM2 mortality equations across various age categories (eTable 8). We provide life expectancy estimates for the general US adult population because previous work has shown that the mortality risk for older adults with T2D approaches that of the general population.[38,39] Life expectancy predictions for ages 65 to 69, 70 to 74, and 75 to 79 y were 14.6, 7.4, and 6.5 y for the original UKPDS equations and 17.4, 11.9, and 6.6 y for calibrated equations. While both original and calibrated equations yielded shorter life expectancies than that of the general population, the calibrated estimates better approximated general population estimates, especially for those 65 to 69 and 70 to 74 y of age.

Complication Rates

In lifetime simulation modeling, individuals receiving treatment with GLP1RA experienced decreased rates of stroke and end-stage renal disease, and those on SGLT2I experienced decreased rates of CHF and MI (Table 2). However, both treatment arms had small

increases (<0.3%) in other complications (e.g., ischemic heart disease, stroke, amputation). This was due to the increased life expectancy of those on treatment with either GLP1RA or SGLT2I and thus increased time to accrue complications. GLP1RAs were associated with gastrointestinal complications in 27.4% of individuals. SGLT2Is were associated with diabetic ketoacidosis and genital infections in 0.4% and 23.2% of individuals, respectively.

Lifetime Outcomes

For the no additional medication arm, the overall NHANES population experienced an average remaining life expectancy of 10.89 LY and 6.55 QALYs (Table 3). However, remaining life expectancy differed widely between the 7 health status categories and generally decreased with increasing Lee index score (Table 3).

Compared with the no additional medication arm, treatment with either GLP1RA or SGLT2I resulted in a higher LY and improved QALY for the overall sample (Table 3). The overall GLP1RA arm experienced +0.29 (95% CI: 0.27–0.31) LYs and +0.15 (0.14, 0.16) QALYs compared with the no additional medication arm. The overall SGLT2I arm experienced +0.26 (0.24, 0.28) LYs and +0.13 (0.12, 0.14) QALYs compared with the no additional medication arm. On average, individuals spent 7.8 and 8.0 y on GLP1RA and SGLT2I, respectively, prior to experiencing an adverse event or death.

For both treatment arms, the youngest age groups with the lowest Lee index score (i.e., 65–74 y with 1–4 points) experienced the greatest magnitude of health improvement with +0.84 (0.75, 0.94) LYs and +0.37 (0.33, 0.42) QALYs for those on GLP1RA and +0.54 (0.44, 0.64) LYs and +0.26 (0.21, 0.30) QALYs for those on SGLT2I. Expected health benefits decreased in a linear manner for older and sicker subgroups. Those with 15+ points on the Lee index (i.e., those with limited life expectancies of 3–3.5 LYs) had the smallest expected benefits equal to or less than +0.05 LYs (3 wk) and +0.03 QALYs (2 wk). Unweighted results (i.e., without NHANES weights to estimate impact on US population) demonstrated similar effectiveness of medications (eTable 9).

Sensitivity Analysis

First, accounting for injection disutility, GLP1RA use was associated with a decrease in QALYs (−0.03 y) for the overall treatment arm and most of the major subgroups (Table 4). We tested the sensitivity of the injection

Table 3 Weighted Average and Incremental Lifetime Outcomes by Treatment Arm across Age and Lee Index Point Categories[a]

		No Additional Medication		GLP1RA		SGLT2I	
		Average LY	Average QALYs	Incremental LY[b]	Incremental QALYs[b]	Incremental LY[b]	Incremental QALYs[b]
	Overall cohort	10.89 (10.88, 10.90)	6.55 (6.54, 6.56)	0.29 (0.27, 0.31)	0.15 (0.14, 0.16)	0.26 (0.24, 0.28)	0.13 (0.12, 0.14)
65–74 y	1–4 points	24.12 (24.05, 24.19)	12.84 (12.81, 12.87)	0.84 (0.75, 0.94)	0.37 (0.33, 0.42)	0.54 (0.44, 0.64)	0.26 (0.21, 0.30)
	5–9 points	15.47 (15.44, 15.51)	8.98 (8.96, 8.99)	0.49 (0.44, 0.53)	0.24 (0.22, 0.26)	0.43 (0.38, 0.47)	0.21 (0.19, 0.23)
	10–14 points	8.28 (8.25, 8.31)	5.23 (5.22, 5.25)	0.14 (0.09, 0.19)	0.08 (0.05, 0.10)	0.15 (0.10, 0.20)	0.08 (0.06, 0.11)
	15+ points	3.68 (3.64, 3.72)	2.46 (2.44, 2.48)	0.05 (0, 0.10)	0.03 (0, 0.06)	0.04 (−0.01, 0.09)	0.03 (0, 0.06)
75+ y[c]	5–9 points	11.79 (11.76, 11.83)	7.25 (7.23,7.26)	0.30 (0.25, 0.34)	0.16 (0.13, 0.18)	0.28 (0.23, 0.33)	0.15 (0.13, 0.18)
	10–14 points	5.98 (5.97, 6)	4.02 (4.01, 4.02)	0.10 (0.09, 0.12)	0.06 (0.05, 0.08)	0.11 (0.10, 0.13)	0.07 (0.06, 0.08)
	15+ points	2.98 (2.97, 3)	2.08 (2.07, 2.09)	0.04 (0.02, 0.05)	0.02 (0.01, 0.03)	0.02 (0, 0.04)	0.02 (0, 0.03)

GLP1RA, glucagon-like peptide 1 receptor agonist; LY, life-years; SGLT2I, sodium-glucose cotransporter 2 inhibitor; QALY, quality-adjusted life-years.
[a]NHANES 2013–2018 MEC weights used to calculate weighted outcomes.
[b]Incremental outcomes are compared with the no additional medication arm.
[c]There were no individuals 75 y or older with 1 to 4 points on the Lee index because those who were at least 75 y old with diabetes were attributed a minimum of 5 points.

Table 4 Sensitivity Analyses: Incremental Lifetime Outcomes for GLP1RA Injection Disutility versus No Additional Medication[a]

		Incremental Life-Years[b]	Incremental QALYs[c]
	Overall Arm	**0.27 (0.26, 0.30)**	**−0.03 (−0.04, −0.02)**
65–74 y	1–4	0.68 (0.59, 0.78)	0.02 (−0.02, 0.06)
	5–9	0.43 (0.38, 0.47)	−0.01 (−0.03, 0.01)
	10–14	0.17 (0.13, 0.22)	−0.05 (−0.07, 0.02)
	15+	0.08 (0.02, 0.13)	−0.03 (−0.06, 0)
75+ y[b]	5–9	0.31 (0.27, 0.36)	−0.03 (−0.05, −0.01)
	10–14	0.11 (0.10, 0.13)	−0.04 (−0.05, −0.03)
	15+	0.04 (0.02, 0.06)	−0.04 (−0.05, −0.02)

GLP1RA, glucagon-like peptide 1 receptor agonist; QALY, quality-adjusted life-years.
[a]NHANES 2013–2018 MEC weights were used to calculate weighted outcomes. Disutility due to injection medication use was −0.031. This was applied annually for every year the participant was on medication, until treatment discontinuation.
[b]There are no individuals 75 years or older with 1 to 4 points on the Lee index because those who are at least 75 with diabetes are attributed a minimum of 5 points.
[c]Incremental outcomes were compared with the no additional medication arm (see Table 3).

disutility parameter and found that QALYs are lowered for the overall population when the disutility is −0.028 or larger (eTable 10). Second, we modeled medication benefit via reductions in risk factors and found a lower absolute benefit (eTable 11). Those with the most limited life expectancy (3–3.5 LYs) had uncertain treatment effects, reflecting the small sample size in NHANES for the oldest and sickest participant subgroups. Next, we modeled the impact of best-case and worst-case event scenarios as well as a baseline HbA1c of 8.0%. We found with each of these analyses that, while the magnitude of health benefits changed, those with the lowest remaining life expectancies continued to experience the smallest QALY gains (eTables 12 and 13). We further reduced the treatment effect of both GLP1RA and SGLT2I use by 75% and 90% to investigate the quality-of-life impact of more conservative treatment assumptions. We found that for the overall population, a 75% reduction in treatment effect yielded an incremental gain from GLP1RA and SGLT2I use of 0.08 (0.06, 0.09) QALYs and 0.05 (0.04, 0.06) QALYs, respectively. At 90% reduction in drug benefit, GLP1RA and SGLY2I use yielded QALY gains of 0.02 (0.01, 0.04) and 0.01 (0, 0.02), respectively. When modeling the use of oral semaglutide, we found this generated the largest absolute benefit across all analytic scenarios for both the average NHANES participant (+1.04 LY, +0.53 QALYs) and across most health categories (eTable 14). Finally, we modeled the impact of drug use in the overall older adults (≥65 y) with T2D, regardless of drug eligibility. We found 751 NHANES 2013–2018 participants meeting this criterion. The lifetime impact of GLP1RA and SGLT2I in this population is larger than the base-case population, given that this population has a longer life expectancy and thus time to accrue drug benefits (eTable 15).

Discussion

Our results indicate that, on average, the older adult population with T2D and CVD will experience significant health benefits from the addition of GLP1RA or SGLT2I. However, the magnitude of expected health benefits varies greatly by age and health status. According to the Second Panel on Cost-Effectiveness in Health and Medicine, a clinically significant difference in health utility between interventions is defined as being ≥0.03.[40] Our study finds that older adults with less than 4 y of remaining life expectancy (those with >15 points on the Lee index) experience quality-of-life benefits from the addition of GLP1RA or SGLT2I that fall below this threshold of clinical significance. While the incremental QALY difference for participants 65 to 74 y and with >15 points on the Lee index is 0.03 QALYs, the modeled CI overlaps with this threshold of clinical significance. Furthermore, when accounting for injection-related disutility associated with GLP1RA, we find that these subgroups are also at risk for harm from treatment. Using NHANES weighting, the older adult subgroup with a Lee index score > 15 represents approximately 8% of the older adult population that is eligible for drug use, or about 400,000 US adults (eTable 4).

In the CVOTs, health benefits from GLP1RA or SGLT2I emerged between 3 and 18 mo after treatment initiation.[41] These trials, however, did not specifically

evaluate geriatric subpopulations nor explicitly weigh the tradeoffs between health benefits and potential adverse events. Furthermore, while observational studies have demonstrated substantial reductions in mortality (>50%) from SGLT2I, these real-world studies lack adequate numbers of the oldest and sickest individuals with T2D and are affected by time-related biases that exaggerate drug benefits.[42–44] We used disease simulation modeling to address these gaps in evidence.

The findings of this study should be considered in relation to recommendations regarding intensive glucose control (HbA1c < 7.0%) and patient heterogeneity. Prior research has concluded that the pursuit of intensive glucose control in older adults with limited life expectancy yields modest health improvement due to the prolonged time to accrual of health benefits (>10 y).[18,45,46] Multiple geriatric diabetes guidelines over the past decade have recommended personalizing care based on individuals' life expectancy, comorbidities, and functional status measures.[47] However, with the advent of GLP1RA and SGLT2I, it has been unclear whether an alternative approach to patient heterogeneity is required. In our study, we still find that there is a threshold of clinical complexity and limited life expectancy (~4 y) beyond which expected benefits are markedly reduced. Future T2D guidelines should consider patient heterogeneity beyond the immediate indications for GLP1RA and SGLT2I.

In addition to prognosis, diabetes treatment guidelines for older adults recommend that patient preferences be considered when devising treatment plans.[18] Previous studies have demonstrated the strong preference for oral versus injectable medications in older populations and suggested that cost-effectiveness analyses in older adults are particularly sensitive to utility assumptions.[48] This study confirms that patient preferences continue to be important with newer diabetes medications, particularly injectable formulations of GLP1RA and in the oldest populations of adults with the most limited life expectancy. We also find there may be a significant health benefit from oral semaglutide use, across health status categories.

Our study has several limitations. We used mortality prediction (Lee index) and T2D forecasting (UKPDS OM2) models that are well established and previously validated.[22–26] Nevertheless, all prediction models have potential limitations. For example, while the Lee index is the gold standard to proxy mortality risk in general populations of older adults, it may not account for specific drivers of mortality in patients with T2D. In addition, the UKPDS model, without calibration, may not reflect secular improvements in diabetes care and life expectancy. Despite these concerns, we have demonstrated the overall face validity of our calibrated model comparing our life expectancy estimates to those from recent US life tables. Ultimately, our goal was to account for the overall impact of advanced age and complex health status on mortality risk, and the Lee index is a reasonable choice for this goal. Second, while we calibrated the UKPDS mortality equation, we did not alter the diabetes-related complication equations in the UKPDS model. Prior study of UKPDS OM2 predictions versus contemporary diabetes populations has shown that UKPDS overpredicts the absolute rate of complications, implying that our model likely also overpredicts complication rates.[28] However, because our article focuses on the *relative* differences in health between SGLT2I and GLP1RA versus no additional medication, we believe that, despite this limitation, our overall findings would be unchanged. Third, because we used treatment estimates from meta-analyses that primarily included trials of younger populations, there is a concern that we might not have captured the true treatment effect in a highly comorbid, older population. However, a recently published meta-analysis showed that while there may be a more pronounced relative treatment benefit in those >65 y compared with <65 y for certain SGLT2I health outcomes (heart failure hospitalizations and stroke), most other important outcomes had no significant difference in treatment effect between the 2 age groups.[17] There was also no significant difference in the relative risk of outcomes between age groups for GLP1RA use. Thus, it is likely reasonable to use the meta-analysis estimates despite differences in population characteristics. Fourth, our study is limited in that it does not include considerations of cost-effectiveness and cannot comment on the opportunity cost of using SGLT2I and GLP1RA in older adults. We purposely focused on modeling the clinical benefits of these drugs because most US Medicare Part D plans already cover GLP1RA and SGLT2.[49] Thus, our primary audience for this article is not payers making decisions whether to cover these medications but rather physicians and older patients deciding to adopt these medicines. Accordingly, our article directly answers the question of whether certain geriatric populations experience no clinically significant health benefit from GLP1RA or SGTL2I. Next, we used NHANES weights to present estimates of GLP1RA and SGLT2I effectiveness in the overall US older adult population. However, because we present results across various subgroups, there is a concern that weighted point estimates may be less precise due to the small sample sizes

of subgroups. Although we used 3 cycles of NHANES surveys to address this issue, we were unable to incorporate earlier cycles due to differences in survey design. We presented 95% CIs to give readers estimates of precision for weighted outcomes. Finally, while our study examines the impact of patient heterogeneity on the treatment benefits of newer diabetes drugs in older adults, we focused on the specific effects of age and functional status. Our study did not account for other important aspects of heterogeneity that may have effects on treatment effect (race/ethnicity, socioeconomic status, access to care, etc.). Future work is needed to incorporate such equity concerns into decision-analytic frameworks.

In conclusion, our model demonstrates that while GLP1RA and SGLT2I are beneficial for the overall population of older adults with diabetes, health benefits diminish to below clinically significant levels in patients with less than 4 y of life expectancy. Accordingly, it remains important to consider heterogeneity in life expectancy and explore patient preferences when weighing the relative benefits of newer diabetes treatments against the potential harm of injection-related disutility and medication adverse events.

Author Contributions

R.S.D., E.H., and W.W. were involved in the development of the study concept and design. All authors were involved in the critical revision of the manuscript. M.R.S. developed the simulation models. R.S.D. calibrated the simulation model, conducted simulation analysis, drafted the manuscript, and had full access to the data in the study. E.H. supervised the study. W.W. assisted with statistical analysis.

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