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Comparison of Semaglutide or Dulaglutide Versus Empagliflozin for Risk for Death and Cardiovascular Outcomes Among Patients With Type 2 Diabetes

Two Target Trial Emulation Studies

Anum Saeed, MD; Suresh R. Mulukutla, MD; Floyd Thoma, BS; Lara Lemon, PhD; Agnes Koczo, MD; Steven Reis, MD; Oscar Marroquin, MD; and Kevin Kip, PhD

Background: Reduction of premature death and adverse cardiovascular outcomes is a key goal in type 2 diabetes management.

Objective: To compare mortality and cardiovascular event risks in patients treated with semaglutide versus empagliflozin and, secondarily, dulaglutide versus empagliflozin.

Design: Target trial emulation studies from observational data comparing semaglutide- or dulaglutide-treated patients with propensity score–matched patients treated with empagliflozin.

Setting: Health care system of 703 academic and community clinical practices.

Participants: Patients aged 45 years or older with type 2 diabetes treated from 1 January 2019 to 31 December 2024 with semaglutide, dulaglutide, or empagliflozin.

Intervention: Initial treatment with semaglutide, dulaglutide, or empagliflozin. At baseline, concomitant treatment with other diabetes medication was permitted, excluding other glucagon-like peptide-1 receptor agonists or sodium–glucose cotransporter-2 inhibitors.

Measurements: A composite of death, myocardial infarction (MI), or stroke was the primary outcome, and secondary composite outcomes included death or MI, MI or stroke, and individual cardiac events.

Results: Patients treated with semaglutide ($n = 7899$) versus empagliflozin ($n = 7899$) were followed for a median of 2.2 years; the respective rates of the composite of death, MI, or stroke were 3.7% versus 4.5% at 2 years and 5.9% versus 6.9% at 3 years. Corresponding incidence rates for the composite outcome were 20.99 versus 23.56 per 1000 person-years, with a hazard ratio (HR) of 0.89 (95% CI, 0.78 to 1.02). The HRs for the individual outcomes were 0.97 (CI, 0.81 to 1.15) for death, 0.85 (CI, 0.68 to 1.05) for MI, and 0.62 (CI, 0.43 to 0.89) for stroke. Risks for dulaglutide- and empagliflozin-treated patients were similar for the composite outcome (HR, 1.03 [CI, 0.90 to 1.16]) and for death, MI, and stroke separately.

Limitation: Observational study design, lack of data on cause-specific mortality, and residual confounding.

Conclusion: Semaglutide treatment seems to confer some advantage over empagliflozin. This advantage was not observed for dulaglutide.

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Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the United States. Although CVD is a generalized public health concern, patients with diabetes mellitus are at nearly double the risk for major adverse cardiovascular events (MACE) (1). Patients with diabetes have a higher likelihood of earlier onset of MACE and worse outcomes than those without diabetes (2, 3). This not only drastically affects patients' quality of life but also has major consequences for productivity and overall health care costs (1). There is an urgent need to optimize allocation and use of preventive treatments in those with diabetes (2).

The advent of newer diabetes management classes, including glucagon-like peptide-1 receptor (GLP-1) agonists, dipeptidyl peptidase-4 inhibitors, and sodium–glucose cotransporter-2 (SGLT-2) inhibitors (4–6), has ushered diabetes management and prevention of MACE into a new era. Both SGLT-2 inhibitors and GLP-1 agonists have shown cardiovascular benefits in patients with type 2 diabetes mellitus and atherosclerotic CVD regardless of hemoglobin A_{1c} (HbA_{1c}) levels (7, 8).

Multisociety guidelines, including from the American Heart Association and American College of Cardiology, now recommend the use of both of these classes regularly for patients with high risk for CVD and diabetes regardless of HbA_{1c} levels. Recent pooled

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data suggest that all-cause mortality and MACE are alleviated with SGLT-2 inhibitors and GLP-1 agonists, but not with dipeptidyl peptidase-4 inhibitors, compared with usual care (9). However, few studies have examined these mechanistically different classes, and specifically the most used drugs in each class, in a head-to-head analysis. Understanding the comparative effectiveness of individual drugs among classes is crucial for precision medicine, which can allow clinicians to tailor treatment on the basis of patient groups. In this study, we did a comparative analysis of the 2 most frequently prescribed GLP-1 agonists, semaglutide (most frequent) and dulaglutide (second most frequent), against empagliflozin, a widely used SGLT-2 inhibitor (10). Using observational data from a large U.S. health care system with community and academic inpatient and outpatient practices, we structured the analysis as 2 hypothetical pragmatic randomized trials to emulate real-world treatment scenarios.

METHODS

Study Design

Using a retrospective observational cohort, we emulated 2 target trials of initial treatment with either semaglutide (primary trial) or dulaglutide (secondary trial) versus empagliflozin among adult patients with type 2 diabetes. The study followed the framework of target trial emulation, which aims to mimic the design and analysis of a hypothetical randomized controlled trial using observational data (11–13). The key study design and analysis components that were used to emulate the target trials are summarized in **Supplement Table 1** (available at Annals.org). The UPMC Quality Improvement Review Committee and Institutional Review Board provided ethical review and approval of the study as an exempt protocol, and all data remained deidentified for this analysis.

Data Sources

We used health-related data captured in the electronic health record (EHR) and ancillary clinical systems, aggregated and harmonized in a clinical data warehouse (14, 15). Specifically, patient information was linked by common identifiers across multiple EHRs, including MediPac, the admit, discharge, and transfer registration and hospital-based billing system; Cerner, the inpatient EHR for relevant clinical information for admitted patients at UPMC inpatient hospitals; and Epic, the UPMC EHR for ambulatory office visits owned by UPMC. For all patients, we accessed sociodemographic data, medical history information (such as comorbid conditions), laboratory results (such as HbA_{1c}), and anthropometric data (such as body mass index) from outpatient encounters. Use of medications was based on prescription orders made by physicians or other prescribers. Deaths were identified using hospital discharge dispositions of "ceased to breathe" sourced from the inpatient medical record system; deaths after hospital discharge were identified via the Death Master File from the Social Security Administration's 2022 National Technical Information Service (16). Our health care system is exempt from the 3-year delay period by the Social Security Administration. Other nonfatal outcomes (such as MI) were obtained from inpatient encounters with diagnoses and procedures coded on the basis of the International Classification of Diseases, Ninth and Tenth Revisions, as previously published by our group (2, 17, 18). Because 97.8% of the source cohort self-declared their race as either Black (10.1%) or White (87.7%), we classified race as Black versus all others. In addition, only 1.5% of patients self-declared their ethnicity as Hispanic; hence, ethnicity was not used in the analyses.

Study Population (Eligibility Criteria)

All selected (eligible) patients had type 2 diabetes; were aged 45 years or older; and had EHR documentation of health care use, comorbid conditions, and recent use of prescription medications (for both diabetes and nondiabetes conditions) at the index prescription visit or at the closest office visit in the prior 5 years. Given very low prescription rates for semaglutide in our system in 2017 and 2018, the index date for patient selection was the first date between 1 January 2019 and 31 December 2024 in which a prescription for semaglutide, dulaglutide, or empagliflozin was documented in the EHR. As a potential washout (look-back) period, this selection was limited to patients without evidence of use of any other GLP-1 agonists or SGLT-2 inhibitors at the index office visit or in the prior 12 months (**Supplement Figure 1**, available at Annals.org). Concomitant use of other diabetes medications (for example, metformin or insulin) was permitted.

Exclusion criteria, which encompassed potential contraindications to semaglutide, dulaglutide, or empagliflozin (**Supplement Figure 1**), included type 1 diabetes, diabetic ketoacidosis, MI or stroke within the prior 6 months, thyroid cancer or family history of thyroid cancer, pancreatitis, multiple endocrine neoplasia syndrome type 2, current pregnancy, estimated glomerular filtration rate below 30 mL/min/1.73 m^2 or recent or current dialysis, and serious illness with an estimated 80% higher risk for death within 90 days (19). The study population was derived from 703 clinical practice groups located in southwestern Pennsylvania, northwestern Pennsylvania or New York, west central Pennsylvania or western Maryland, and north central Pennsylvania.

Treatment Strategies

Patients were classified as treated initially with either semaglutide or empagliflozin (primary trial) or dulaglutide or empagliflozin (secondary trial).

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Table 1. Comparison of Characteristics of Patients Treated With Semaglutide Versus Empagliflozin Before and After Matching*

Characteristic	Unmatched			Matched		
	Semaglutide (*n* = 14 068)	Empagliflozin (*n* = 13 154)	SMD†	Semaglutide (*n* = 7899)	Empagliflozin (*n* = 7899)	SMD†
Location of clinical practice	–	–	–	–	–	0.00*
Altoona	1840 (13.1)	1233 (9.4)	0.12	867 (11.0)	867 (11.0)	–
Center for Integrative Medicine	5569 (39.6)	5187 (39.4)	0.003	3144 (39.8)	3144 (39.8)	–
Cole	179 (1.4)	232 (1.8)	0.04	88 (1.1)	88 (1.1)	–
Erie Physicians Network	58 (0.4)	90 (0.7)	0.04	30 (0.4)	30 (0.4)	–
Fayette Physician Network	14 (0.1)	76 (0.6)	0.08	10 (0.1)	10 (0.1)	–
Great Lakes Physician Practice	763 (5.4)	340 (2.6)	0.14	276 (3.5)	276 (3.5)	–
Renaissance Family Practice	309 (2.2)	374 (2.8)	0.04	139 (1.8)	139 (1.8)	–
Soldiers and Sailors	28 (0.2)	17 (0.1)	0.02	6 (0.1)	6 (0.1)	–
Somerset	278 (2.0)	462 (3.5)	0.09	210 (2.7)	210 (2.7)	–
Susquehanna Health	863 (6.1)	800 (6.1)	0.002	531 (6.7)	531 (6.7)	–
UPMC Hamot Regional Health Management System	1387 (9.9)	1476 (11.2)	0.04	860 (10.9)	860 (10.9)	–
University of Pittsburgh Physicians	2081 (14.8)	2342 (17.8)	0.08	1419 (18.0)	1419 (18.0)	–
Western Maryland	352 (2.5)	145 (1.1)	0.10	116 (1.5)	116 (1.5)	–
All others	347 (2.5)	381 (2.9)	0.03	203 (2.6)	203 (2.6)	–
Year started semaglutide or empagliflozin treatment	–	–	–	–	–	0.00*
2019	770 (5.5)	1604 (12.2)	0.24	645 (8.2)	645 (8.2)	–
2020	853 (6.1)	1553 (11.8)	0.20	685 (8.7)	685 (8.7)	–
2021	1911 (13.6)	2125 (16.1)	0.07	1331 (16.9)	1331 (16.9)	–
2022	2532 (18.0)	2561 (19.5)	0.04	1536 (19.4)	1536 (19.4)	–
2023	3690 (26.2)	2494 (19.0)	0.17	1728 (21.9)	1728 (21.9)	–
2024	4312 (30.6)	2817 (21.4)	0.21	1974 (25.0)	1974 (25.0)	–
Health plan member	5467 (38.9)	5561 (42.3)	0.07	3215 (40.7)	3215 (40.7)	0.00*
Mean age (SD), *y*	62.1 (9.5)	66.2 (10.3)	0.42	63.7 (9.6)	64.4 (9.9)	0.07
Female	8024 (57.0)	5105 (38.8)	0.37	3874 (49.0)	3625 (45.9)	0.06
Black race	1286 (9.1)	1322 (10.1)	0.03	786 (10.0)	803 (10.2)	0.01
Commercial insurance	7709 (54.8)	6013 (45.7)	0.18	4019 (50.9)	3946 (50.0)	0.02
Medicare	6037 (42.9)	7243 (55.1)	0.25	3769 (47.7)	3926 (49.7)	0.04
Mean area deprivation index (SD)	68.2 (22.3)	66.9 (22.9)	0.06	67.7 (22.3)	67.4 (22.9)	0.01
Physician office visits in past year						
None	937 (6.7)	924 (7.0)	0.01	544 (6.9)	576 (7.3)	0.004
1 or 2	3736 (26.6)	3525 (26.8)	0.01	2082 (26.4)	2075 (26.3)	0.001
3–6	5430 (38.6)	5286 (40.2)	0.03	3065 (38.8)	3171 (40.1)	0.01
≥7	3965 (28.2)	3419 (26.0)	0.05	2208 (27.9)	2077 (26.3)	0.02
ED visit in past year	457 (3.2)	506 (3.8)	0.03	272 (3.4)	274 (3.5)	0.001
Mean body mass index (SD), kg/m^2	37.0 (7.2)	33.0 (6.5)	0.59	35.2 (6.5)	34.4 (6.6)	0.14
Mean diastolic blood pressure (SD), *mm Hg*	78.2 (8.5)	76.8 (9.1)	0.17	77.8 (8.6)	77.5 (9.0)	0.02
Mean hemoglobin A_{1c} (SD), *%*	7.2 (1.6)	7.6 (1.5)	0.31	7.5 (1.6)	7.5 (1.5)	0.05
Medication use						
ACE inhibitor	5560 (39.5)	5854 (44.5)	0.10	3368 (42.6)	3397 (43.0)	0.01
Angiotensin receptor–neprilysin inhibitor	77 (0.5)	569 (4.3)	0.25	75 (0.9)	65 (0.8)	0.01
β-Blocker	4770 (33.9)	5854 (44.5)	0.20	2997 (37.9)	3050 (38.6)	0.01
Insulin	3133 (22.3)	2749 (20.9)	0.03	1916 (24.3)	1879 (23.7)	0.01
Metformin	9650 (68.6)	9534 (72.5)	0.09	5660 (71.7)	5692 (72.1)	0.01
Statin	10 847 (77.1)	11 192 (85.1)	0.21	6444 (81.6)	6583 (83.3)	0.05
Sulfonylurea	2891 (20.6)	3851 (29.3)	0.20	2031 (25.7)	2131 (27.0)	0.03
Charlson Comorbidity Index						
CHF	1007 (7.2)	2487 (18.9)	0.35	833 (10.5)	857 (10.8)	0.01
COPD	3923 (35.0)	3884 (29.5)	0.12	2622 (33.2)	2447 (31.0)	0.05
Dementia	91 (0.6)	135 (1.0)	0.04	66 (0.8)	72 (0.9)	0.01
Diabetes with comorbid conditions	4654 (33.1)	5874 (44.7)	0.24	3117 (39.5)	3215 (40.7)	0.03
Elixhauser Comorbidity Index						
Depression	3481 (24.7)	2451 (18.6)	0.15	1743 (22.1)	1646 (20.8)	0.03
Hypothyroidism	2970 (21.1)	2315 (17.6)	0.09	1564 (19.8)	1450 (18.4)	0.04
Liver disease	2417 (17.2)	1841 (14.0)	0.09	1268 (16.1)	1231 (15.6)	0.01
Lymphoma	68 (0.5)	121 (0.9)	0.05	51 (0.6)	43 (0.5)	0.01
Peripheral vascular disease	1138 (8.1)	1482 (11.3)	0.11	738 (9.3)	750 (9.5)	0.01
Rheumatoid arthritis	1178 (8.4)	811 (6.2)	0.09	582 (7.4)	538 (6.8)	0.02
Valvular disease	986 (7.0)	1520 (11.6)	0.16	643 (8.1)	680 (8.6)	0.02

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Table 1–Continued

Characteristic	Unmatched			Matched		
	Semaglutide (*n* = 14 068)	Empagliflozin (*n* = 13 154)	SMD†	Semaglutide (*n* = 7899)	Empagliflozin (*n* = 7899)	SMD†
Mean Charlson Comorbidity Index total score (SD)	2.5 (1.6)	2.9 (1.8)	0.25	2.6 (1.7)	2.6 (1.7)	0.003
Elixhauser AHRQ score						
Quartile 1	5081 (36.1)	3190 (24.3)	0.26	2451 (31.0)	2334 (29.6)	0.01
Quartile 2	3148 (22.4)	2697 (20.5)	0.05	1758 (22.3)	1755 (22.2)	0.001
Quartile 3	3410 (24.2)	3676 (27.9)	0.09	2082 (26.4)	2157 (27.3)	0.01
Quartile 4	2429 (17.3)	3591 (37.3)	0.24	1608 (20.4)	1653 (20.9)	0.01

ACE = angiotensin-converting enzyme; AHRQ = Agency for Healthcare Research and Quality; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; ED = emergency department; SMD = standardized mean difference.
* Values are numbers (percentages) unless otherwise indicated. All variables were used in the propensity score model.
† Presented as absolute value.

Study Outcomes and Follow-up

The primary outcome was risk for the composite outcome of death, MI, or stroke over the longitudinal follow-up period that ended 31 December 2024. Secondary outcomes included the individual end points of all-cause death, MI, stroke, heart failure (HF), and atrial fibrillation, as well as the composite outcomes death or MI; MI or stroke; and any CVD event, defined as MI, stroke, HF, or atrial fibrillation. Tertiary outcomes included change in body weight and HbA_{1c} at 6 and 12 months. The follow-up period for the analysis started on the day after the index date (first day after the prescription for semaglutide, dulaglutide, or empagliflozin).

Statistical Analysis

We compared sociodemographic and clinical characteristics in patients treated with semaglutide or dulaglutide versus empagliflozin (before and after matching) using standardized mean differences (SMDs). We selected empagliflozin-treated patients matched to either semaglutide- or dulaglutide-treated patients using propensity score (PS) methods (20, 21). Specifically, we used PSs from a logistic regression model fitted with classification into the semaglutide or dulaglutide group as the response variable and inclusion of explanatory variables. Separate PS models were fitted for the primary analysis of semaglutide versus empagliflozin (**Table 1**) and secondary analysis of dulaglutide versus empagliflozin (**Supplement Table 2**, available at Annals.org). We used 1:1 PS greedy nearest-neighbor matching without replacement within a caliper width of 0.25 to construct the matched treated and nontreated groups. We matched patients directly on year of index treatment, clinical practice group, and membership or nonmembership in the UPMC health (insurance) plan. The latter was done for the theoretical (unknown) possibility of potential differences in provision of care, along with potential more thorough ascertainment of health status and clinical outcomes among UPMC health plan members (that is, patients most likely to use UPMC treatment facilities). We considered in the PS models the ZIP code–level area deprivation index, a validated neighborhood-level measure that is consistently associated with health outcomes (22).

From the matched groups, we used the Kaplan–Meier method to estimate incidence proportions (expressed as percentages) by initial treatment at 1, 2, and 3 years of follow-up. Incidence rates and incidence rate differences per 1000 person-years (with 95% CIs) were also calculated, along with corresponding hazard ratios (HRs) and 95% CIs. Because the propensity-matched treatment groups were generally well matched, no additional covariates were used for adjustment (that is, for potential residual confounding).

Missing values for key covariates with less than 15% missing at baseline were imputed using median values (**Supplement Table 3**, available at Annals.org). A recent HbA_{1c} value was missing in 28% of patients at baseline. Because this measure was viewed as critical for patient matching in the PS model by treatment received, the PS model included an indicator variable for missing, with remaining indicator variables of 4.0% to 5.6%, 5.7% to 6.4%, 6.5% to 8.0%, and greater than 8.0% (with missing coded as 0%). Assuming that HbA_{1c} values were missing at random, this approach seemed to be successful because HbA_{1c} values among matched patients with nonmissing HbA_{1c} values were nearly identical by treatment group (**Table 1**).

Exploratory subgroup analyses (that is, hypothesis-generating) were done, including by age (45 to 64 vs. ≥65 years); sex (female vs. male); treatment-naive (no vs. yes), defined as no use of the index medication before the 12-month look-back period; UPMC health plan member (no vs. yes); body mass index at baseline (<35 vs. ≥35 kg/m^2); HbA_{1c} at baseline (<7% vs. ≥7%); insulin use at baseline (no vs. yes); metformin use at baseline (no vs. yes); and history of MI or cerebrovascular accident (no vs. yes). For all subgroup analyses, separate PS models were fitted to account for the specific characteristics most associated with imbalance by initial treatment received (**Supplement Table 4**, available at Annals.org). Cox proportional hazard models were fitted to formally test for interaction among subgroups. **Supplement Table 5** (available at Annals.org) provides PS model results for all subgroups, as well as the primary and secondary target trial cohorts. A sensitivity analysis was done stratified by primary geographic location of the 703 clinical practice groups (**Supplement Table 6**, available at Annals.org).

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Table 2. Primary and Secondary Outcomes in 1:1 PS-Matched Cohorts for Semaglutide Versus Empagliflozin and Dulaglutide Versus Empagliflozin

Outcome of Interest	Semaglutide vs. Empagliflozin		Dulaglutide vs. Empagliflozin	
	Semaglutide	Empagliflozin	Dulaglutide	Empagliflozin
Death/MI/stroke (primary outcome)				
Events/patients at risk, *n/N*	398/7899	450/7899	494/6093	482/6093
Median follow-up (IQR), *y*	2.20 (1.06 to 3.47)	2.17 (1.07 to 3.53)	3.02 (1.80 to 4.54)	3.04 (1.80 to 4.56)
IR per 1000 PY	20.99	23.56	25.64	25.02
Rate difference per 1000 PY (95% CI)	−2.56 (−5.56 to 0.44)	Reference	0.62 (−2.55 to 3.80)	Reference
HR (95% CI)	0.89 (0.78 to 1.02)	Reference	1.03 (0.90 to 1.16)	Reference
Death				
Events/patients at risk, *n/N*	260/7899	272/7899	324/6093	300/6093
Median follow-up (IQR), *y*	2.24 (1.09 to 3.53)	2.22 (1.09 to 3.58)	3.10 (1.87 to 4.61)	3.12 (1.87 to 4.63)
IR per 1000 PY	13.50	13.98	16.47	15.24
Rate difference per 1000 PY (95% CI)	−0.49 (−2.82 to 1.85)	Reference	1.22 (−1.26 to 3.71)	Reference
HR (95% CI)	0.97 (0.81 to 1.15)	Reference	1.08 (0.92 to 1.27)	Reference
MI				
Events/patients at risk, *n/N*	147/7899	175/7899	173/6093	171/6093
Median follow-up (IQR), *y*	2.20 (1.07 to 3.48)	2.18 (1.07 to 3.55)	3.03 (1.82 to 4.56)	3.06 (1.82 to 4.58)
IR per 1000 PY	7.73	9.12	8.93	8.83
Rate difference per 1000 PY (95% CI)	−1.39 (−3.24 to 0.45)	Reference	0.10 (−1.77 to 1.98)	Reference
HR (95% CI)	0.85 (0.68 to 1.05)	Reference	1.01 (0.82 to 1.25)	Reference
Stroke				
Events/patients at risk, *n/N*	46/7899	75/7899	81/6093	84/6093
Median follow-up (IQR), *y*	2.22 (1.08 to 3.51)	2.20 (1.08 to 3.58)	3.08 (1.84 to 4.60)	3.10 (1.85 to 4.60)
IR per 1000 PY	2.40	3.87	4.14	4.30
Rate difference per 1000 PY (95% CI)	−1.48 (−2.59 to −0.36)	Reference	−0.15 (−1.44 to 1.13)	Reference
HR (95% CI)	0.62 (0.43 to 0.89)	Reference	0.97 (0.71 to 1.31)	Reference
Death/MI				
Events/patients at risk, *n/N*	368/7899	404/7899	446/6093	430/6093
Median follow-up (IQR), *y*	2.20 (1.07 to 3.48)	2.18 (1.07 to 3.55)	3.03 (1.82 to 4.56)	3.06 (1.82 to 4.58)
IR per 1000 PY	19.35	21.06	23.02	22.19
Rate difference per 1000 PY (95% CI)	−1.71 (−4.56 to 1.14)	Reference	0.82 (−2.17 to 3.82)	Reference
HR (95% CI)	0.92 (0.80 to 1.06)	Reference	1.04 (0.91 to 1.19)	Reference
MI/stroke				
Events/patients at risk, *n/N*	186/7899	230/7899	243/6093	236/6093
Median follow-up (IQR), *y*	2.20 (1.06 to 3.47)	2.17 (1.07 to 3.53)	3.02 (1.80 to 4.54)	3.04 (1.80 to 4.56)
IR per 1000 PY	9.81	12.04	12.61	12.25
Rate difference per 1000 PY (95% CI)	−2.23 (−4.33 to −0.13)	Reference	0.37 (−1.86 to 2.59)	Reference
HR (95% CI)	0.81 (0.67 to 0.99)	Reference	1.03 (0.86 to 1.23)	Reference
Heart failure				
Events/patients at risk, *n/N*	307/7899	341/7899	319/6093	307/6093
Median follow-up (IQR), *y*	2.16 (1.03 to 3.45)	2.13 (1.05 to 3.52)	2.99 (1.77 to 4.53)	3.03 (1.77 to 4.55)
IR per 1000 PY	16.35	17.96	16.68	16.02
Rate difference per 1000 PY (95% CI)	−1.61 (−4.28 to 1.04)	Reference	1.65 (−1.91 to 3.22)	Reference
HR (95% CI)	0.91 (0.78 to 1.06)	Reference	1.04 (0.89 to 1.22)	Reference
Atrial fibrillation				
Events/patients at risk, *n/N*	71/7899	78/7899	85/6093	68/6093
Median follow-up (IQR), *y*	2.22 (1.08 to 3.51)	2.20 (1.08 to 3.56)	3.01 (1.84 to 4.58)	3.10 (1.84 to 4.60)
IR per 1000 PY	3.71	4.04	4.36	3.48
Rate difference per 1000 PY (95% CI)	−0.33 (−1.57 to 0.92)	Reference	0.88 (−0.36 to 2.12)	Reference
HR (95% CI)	0.92 (0.66 to 1.26)	Reference	1.25 (0.91 to 1.72)	Reference
Any cardiac event				
Events/patients at risk, *n/N*	585/7899	667/7899	631/6093	643/6093
Median follow-up (IQR), *y*	2.60 (1.99 to 3.37)	2.06 (1.00 to 3.43)	2.87 (1.65 to 4.41)	2.91 (1.66 to 4.42)
IR per 1000 PY	31.97	36.19	34.14	34.77
Rate difference per 1000 PY (95% CI)	−4.22 (−8.00 to −0.45)	Reference	−0.63 (−4.41 to 3.16)	Reference
HR (95% CI)	0.88 (0.79 to 0.99)	Reference	0.98 (0.88 to 1.10)	Reference

HR = hazard ratio; IR = incidence rate; MI = myocardial infarction; PS = propensity score; PY = person-years.

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We used SAS, version 9.4 (SAS Institute), for all analyses.

Role of the Funding Source

The American Heart Association had no role in the study's design, data collection, analysis, or manuscript preparation.

RESULTS

Baseline Characteristics

Before 1:1 PS matching, the mean age was 62.1 years among 14 068 patients treated with semaglutide and 66.2 years among 13 154 treated with empagliflozin (Table 1). From 2019 to 2024, use of semaglutide generally increased. Other substantial differences before matching (SMD ≥0.30) for semaglutide-treated patients included higher prevalence of female sex (57.0% vs. 38.8%), higher mean body mass index (37.0 vs. 33.0 kg/m^2), lower mean HbA_{1c} (7.2% vs. 7.6%), and lower prevalence of congestive HF (7.2% vs. 18.9%). The prevalence of comorbid conditions was generally lower in patients receiving semaglutide.

After 1:1 matching of 7899 patients treated with semaglutide and 7899 treated with empagliflozin, distributions of baseline characteristics were similar except for nominally higher body mass index in semaglutide- than empagliflozin-treated patients (35.2 vs. 34.4 kg/m^2; SMD, 0.14). The median length of follow-up among matched patients who did not die was 2.3 years (IQR, 1.1 to 3.5 years) in semaglutide-treated patients versus 2.2 years (IQR, 1.1 to 3.6 years) in empagliflozin-treated patients. In the secondary trial analysis, after 1:1 PS matching of 6093 patients treated with dulaglutide and 6093 treated with empagliflozin, distributions of baseline characteristics were similar by treatment regimen (SMD <0.10 for all characteristics) (Supplement Table 2).

Primary Trial Results

Treatment History

For semaglutide-treated patients, rates of continued medication use based on available follow-up data at 6, 12, and 18 months were 75.1%, 64.6%, and 59.1%, respectively. Among these patients, corresponding rates of dulaglutide use were 5.3%, 7.4%, and 8.3% and corresponding rates of empagliflozin use were 3.8%, 6.5%, and 9.2%. For empagliflozin-treated patients, rates of continued medication use at 6, 12, and 18 months were 80.1%, 71.9%, and 67.4%, respectively. Among these patients, corresponding rates of semaglutide use were 4.8%, 8.8%, and 12.0% and corresponding rates of dulaglutide use were 2.2%, 4.2%, and 5.8%.

Effect of Semaglutide Versus Empagliflozin on Weight Loss and Glycemic Control

Mean changes in weight at 6 and 12 months were −3.6 kg (SD, 6.2) and −4.3 kg (SD, 7.6), respectively, for patients treated with semaglutide and −2.6 kg (SD, 5.1) and −3.2 kg (SD, 6.2), respectively, for those treated with empagliflozin. Mean changes in HbA_{1c} at 6 and 12 months were −0.43 percentage point (SD, 1.37) and −0.34 percentage point (SD, 1.52), respectively, for patients treated with semaglutide and −0.21 percentage point (SD, 1.21) and −0.18 percentage point (SD, 1.32), respectively, for those treated with empagliflozin.

Effect of Semaglutide Versus Empagliflozin on MACE and Mortality

For the primary outcome, our results indicated a nominally lower cumulative incidence of death, MI, or stroke with the use of semaglutide versus empagliflozin starting at about 1 year of follow-up (Figure 1). Respective rates of death, MI, or stroke were 1.9% versus 2.2% at 1 year, 3.7% versus 4.5% at 2 years, and 5.9% versus 6.9% at 3 years. The incidence rate per 1000 person-years was 20.99 for semaglutide, compared with 23.56 for empagliflozin (Table 2, *left*). This resulted in a rate difference of −2.56 (95% CI, −5.56 to 0.44) and HR of 0.89 (CI, 0.78 to 1.02). For the 7 secondary outcomes, all risk estimates were in the direction favoring use of semaglutide, with the lowest semaglutide-associated relative risks for stroke (HR, 0.62 [CI, 0.43 to 0.89]) and MI or stroke (HR, 0.81 [CI, 0.67 to 0.99]).

Exploratory Subgroup Analyses

Most subgroups examined with respect to risk for death, MI, or stroke yielded estimates in the direction that nominally favored treatment with semaglutide over empagliflozin (Supplement Figure 2, available at Annals.org). In the subgroups examined, the risk for death, MI, or stroke in relation to use of semaglutide was numerically lower among patients younger than 65 years (HR, 0.76 [CI, 0.61 to 0.96]) than among patients aged 65 years or older (HR, 1.02 [CI, 0.86 to 1.22]) (Supplement Figure 1). The risk for death, MI, or stroke in relation to use of semaglutide was also lower among patients with an HbA_{1c} below 7% (HR, 0.74 [CI, 0.56 to 0.97]) than among patients with an HbA_{1c} of 7% or higher (HR, 0.98 [CI, 0.81 to 1.19]).

Sensitivity Analysis

When the 703 clinical practice groups were categorized into 4 separate large geographic regions, the apparent lower risk for death, MI, or stroke associated with semaglutide was evident only among patients treated in clinical practices in southwestern Pennsylvania (HR, 0.75 [CI, 0.63 to 0.90]) (Supplement Table 6). In secondary analyses, patients from southwestern Pennsylvania (59.7% of the total sample), compared with all other locations, were more likely to self-report Black race (15.3% vs. 2.3%) and have higher indicators of access to health care, including higher enrollment in the UPMC health insurance plan (51.1% vs. 25.3%), higher use of telemedicine for office visits (15.4% vs. 3.5%), and higher annual median income ($53 992 vs. $45 644).

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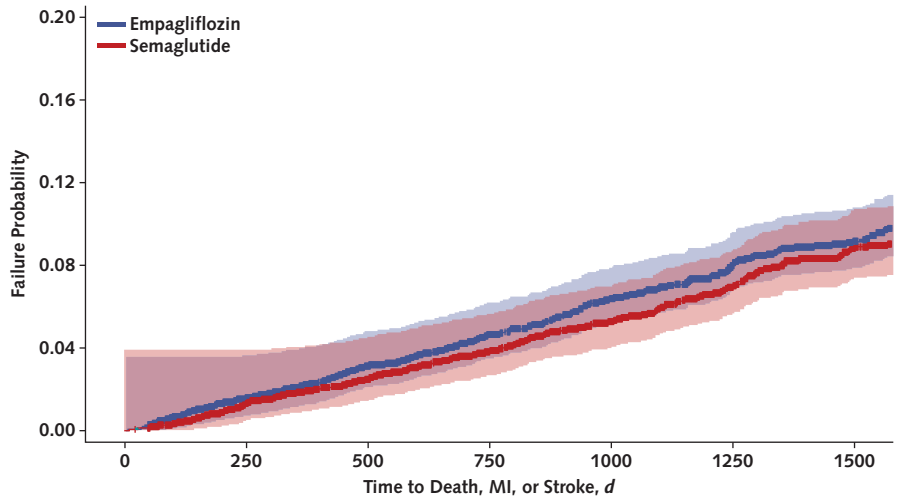
Figure 1. Kaplan–Meier cumulative incidence curves of the risk for death/MI/stroke, by initial treatment with either semaglutide (*red*) or empagliflozin (*blue*).



MI = myocardial infarction.

Secondary Trial Results: Effect of Dulaglutide Versus Empagliflozin on Weight Loss, Glycemic Control, MACE, and Mortality

Mean changes in weight at 6 and 12 months were −2.0 kg (SD, 5.3) and −2.8 kg (SD, 6.7), respectively, for patients treated with dulaglutide and −2.4 kg (SD, 5.1) and −3.0 kg (SD, 6.2), respectively, for those treated with empagliflozin. Mean changes in HbA_{1c} at 6 and 12 months were −0.28 percentage point (SD, 1.40) and −0.25 percentage point (SD, 1.56), respectively, for patients treated with dulaglutide and −0.27 percentage point (SD, 1.31) and −0.27 percentage point (SD, 1.44), respectively, for those treated with empagliflozin.

The risk for death, MI, or stroke over follow-up was similar for patients treated with dulaglutide versus empagliflozin (**Figure 2**). Respective rates of death, MI, or stroke were 2.1% versus 2.4% at 1 year, 5.1% versus 4.5% at 2 years, and 8.1% versus 7.8% at 3 years. The incidence rate per 1000 person-years was 25.64 for dulaglutide-treated patients versus 25.02 for empagliflozin-treated patients (**Table 2**, *right*), with a corresponding HR of 1.03 (CI, 0.90 to 1.16) (**Table 2**, *right*). For the remaining secondary outcomes, the direction of cardiac risk estimates was mixed by treatment regimen, and none of the 95% CIs excluded the null value (0.0 for risk difference, 1.0 for HR).

Discussion

In these head-to-head emulated target trials examining possible cardiovascular benefits of either semaglutide or dulaglutide versus empagliflozin among adult patients with type 2 diabetes aged 45 years and older from a large network of more than 700 clinical practice groups, we report 4 key findings. First, although subgroup estimates were imprecise, our results suggest that treatment with semaglutide (vs. empagliflozin) may be more beneficial for our primary composite outcome of death, MI, or stroke after an average of approximately 2 years of treatment, particularly among patients younger than 65 years. Second, this potential treatment advantage with semaglutide was largely driven by a clear lower risk for stroke (and potentially slight advantage over other cardiovascular outcomes) but not a clear lower risk for death. Third, treatment with dulaglutide (the second most prevalent GLP-1 agonist in this health care system) does not seem to confer any meaningful benefit over treatment with empagliflozin. Finally, the apparent modest treatment benefit of semaglutide over empagliflozin coincided with modest greater reductions in weight and HbA_{1c} within the first year of use. In aggregate, our findings are directly applicable to populations mostly of White race, with a low proportion of Hispanic ethnicity.

Consistent with a recent report by Lingvay and colleagues (23), semaglutide users in our study showed a greater weight loss and HbA_{1c} reduction than those receiving empagliflozin. Similarly, in the STEP-HFpEF (Semaglutide Treatment Effect in People with Obesity and HFpEF [HF with preserved ejection fraction]) trial, semaglutide improved HF-related symptoms, physical limitations, and exercise function, as well as levels of N-terminal pro–B-type natriuretic peptide, with the magnitude of benefit directly related to the extent of weight loss (24). It is thus plausible that the greater

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reduction in cardiovascular events (for example, MI or stroke) that we observed is explained at least in part by the weight loss and more robust glycemic control achieved by semaglutide users.

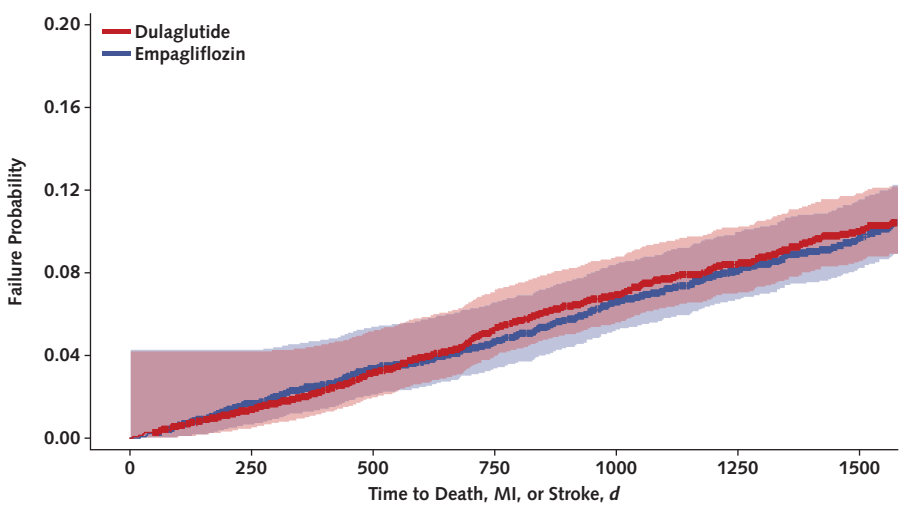
Although both GLP-1 agonists and SGLT-2 inhibitors have demonstrated efficacy in glycemic control, weight management, and cardiovascular benefits, they have different mechanisms of action and may confer distinct clinical advantages in different patient populations (25, 26). The latest clinical guidelines by the American College of Physicians (27) uphold such differences and, to date, offer several individualized recommendations for use of GLP-1 agonists and SGLT-2 inhibitors. However, more mechanistic and population-based data may be able to help delineate specific precision medicine approaches, especially with wider uptake and promising newer agents currently in advanced phases of clinical trials (28). In this regard, the current head-to-head analyses were done to potentially affect clinical decision making and optimize precision medicine initiatives.

At a molecular level, GLP-1 agonists stabilize endothelial function, reduce inflammation, and decrease oxidative stress (21, 22). However, we did not find superior effects in preventing the primary or HF outcome when comparing dulaglutide (second most commonly used GLP-1 in our health care system) versus empagliflozin. Although semaglutide and dulaglutide share the same primary mechanism of action with GLP-1 receptor agonists, several mechanisms may explain the possible superior cardiovascular profile of the former drug. Semaglutide has a consistently more pronounced effect on weight loss and glycemic control than dulaglutide in head-to-head comparisons (29–31). In addition, semaglutide has potent anti-inflammatory effects (32) and significantly reduced high-sensitivity C-reactive protein levels in patients with obesity (33), diabetes mellitus, or HF with preserved ejection fraction (34). Although no head-to-head comparisons are available between semaglutide and dulaglutide, recent data indicate that reductions in high-sensitivity C-reactive protein levels are more pronounced with semaglutide than with empagliflozin and other GLP-1 agonists (35).

Our suggestion of potential greater benefit in cardiovascular adverse outcome reductions among younger (<65 years) patients with semaglutide use warrants future investigation. One plausible explanation of this finding may be that there is more pronounced improvement in endothelial function, inflammation (36), and myocardial hemodynamics (37) in younger patients due to their generally better baseline cardiovascular health and greater capacity for physiologic adaptation. Further, younger patients generally have a better cardiovascular risk profile (38) and shorter exposure to these risk factors, which could influence a more meaningful semaglutide effect (39, 40). Younger patients may have better medication adherence due to more tolerance of the potential side effects of semaglutide than older patients. These reasons may explain the suggestion of greater benefit of semaglutide among younger patients in our study.

Finally, our data indicate a pronounced geographic influence on semaglutide outcomes among patients who had substantially greater access to health care,

Figure 2. Kaplan-Meier cumulative incidence curves of the risk for death/MI/stroke, by initial treatment with either dulaglutide (*red*) or empagliflozin (*blue*).



MI = myocardial infarction.

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including higher insurance coverage, telemedicine use, and income. This suggests that regional differences likely stem from previously observed (41) disparities in health care access rather than a true geographic variation in treatment effect.

Our study has limitations. First, we could not assess cause-specific mortality, which would have provided additional insight into the relationship between diabetes treatment regimen and risk for CVD mortality. Second, classification of index medication use (semaglutide, empagliflozin, or dulaglutide) was based on prescription orders rather than prescriptions that were filled and did not account for the extent of adherence to filled prescriptions. Our suspicion is that any potential misclassification on medication use would tend to be nondifferential and bias results toward the null (no treatment association). Third, hospitalizations (such as for treatment of MI) that occurred outside the UPMC system were not captured in our analyses. However, because UPMC retains about 80% of its patient population, changes due to missing patient population may not be substantial. Furthermore, similar results were observed in the subgroup analysis of UPMC health plan members only (that is, the patients most likely to be treated in UPMC facilities). Finally, residual confounding may be present in our analysis.

In conclusion, among adult patients aged 45 years or older with type 2 diabetes, treatment with semaglutide seems to modestly lower the risk for our composite end point of death, MI, or stroke compared with treatment with empagliflozin; this finding was primarily driven by reductions in stroke and to a lesser degree MI risk. The advantage of semaglutide seems to be more evident among patients younger than 65 years and those with greater access to health care. Dulaglutide does not seem to confer a clinical treatment advantage over empagliflozin.

From School of Medicine, University of Pittsburgh, and Heart and Vascular Institute, UPMC, Pittsburgh, Pennsylvania (A.S., A.K., S.R., O.M.); School of Medicine, University of Pittsburgh; Heart and Vascular Institute, UPMC; and Clinical Analytics, UPMC, Pittsburgh, Pennsylvania (S.R.M.); Heart and Vascular Institute, UPMC, Pittsburgh, Pennsylvania (F.T.); and Clinical Analytics, UPMC, Pittsburgh, Pennsylvania (L.L., K.K.).

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Corresponding Author: Anum Saeed, MD, UPMC Heart and Vascular Institute, University of Pittsburgh School of Medicine, 200 Lothrop Street, BST Building 1055W, Pittsburgh, PA 15213; e-mail, saeeda@pitt.edu.

Author contributions are available at Annals.org.

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Author Contributions: Conception and design: A. Saeed, K. Kip.
Analysis and interpretation of the data: S.R. Mulukutla, L. Lemon, K. Kip.
Drafting of the article: A. Saeed, L. Lemon, A. Koczo, S. Reis, K. Kip.
Critical revision for important intellectual content: A. Saeed, S.R. Mulukutla, L. Lemon, O. Marroquin, K. Kip.
Final approval of the article: A. Saeed, S.R. Mulukutla, F. Thoma, L. Lemon, A. Koczo, S. Reis, O. Marroquin, K. Kip.
Statistical expertise: L. Lemon, K. Kip.
Collection and assembly of data: S.R. Mulukutla, F. Thoma, K. Kip.

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