External Control Arm with Real-World Data to Assess the Effect of Semaglutide on Chronic Kidney Disease Risk among Patients with Type 2 Diabetes

Onur Baser, MA, MS, PhD[1]; Nehir Yapar[2]; Katarzyna Rodchenko, MA, MPH[2]; Munira Mohamed, MPH[2]; Alexandra Passarelli, MPH[2]; Shuangrui Chen, MS[2]; Yuanqing Lu, MS[2]

[1]Graduate School of Public Health, City University of New York (CUNY), New York, NY; [2]Columbia Data Analytics, New York, NY

BACKGROUND

Chronic kidney disease (CKD) affects approximately 14% of the adult population.[1] The condition is often underdiagnosed, with up to 9 of 10 affected individuals unaware they have CKD.[2] Type 2 diabetes mellitus (T2DM) is a leading cause of CKD.[3] The coexistence of T2DM and CKD presents a significant clinical challenge, as individuals with both conditions often experience accelerated disease progression and greater healthcare burdens.[4]

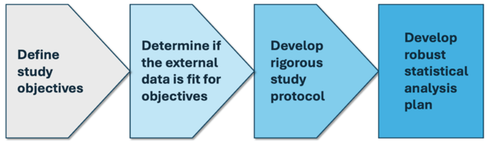
Despite advances in treatment choices, many patients continue to experience kidney function decline, often culminating in kidney failure or death, predominantly due to cardiovascular complications.[5] Recently, the FLOW trial, a landmark study using 3,533 participants (ClinicalTrials.gov No. 03819153), evaluated the efficacy and safety of semaglutide, a GLP-1 receptor agonist, and found it protective in preventing kidney failure, substantial kidney function loss, and death from kidney-related or cardiovascular causes in patients with T2DM and CKD.[6]

OBJECTIVES

Since the real-world effectiveness and long-term outcomes associated with semaglutide treatment remain insufficiently characterized, particularly outside the controlled environment of RCTs, this study leveraged data from Kythera Labs to construct an external control arm (ECA) based on the FLOW trial's inclusion and exclusion criteria, providing a comprehensive evaluation of semaglutide's renoprotective effects in a real-world setting.

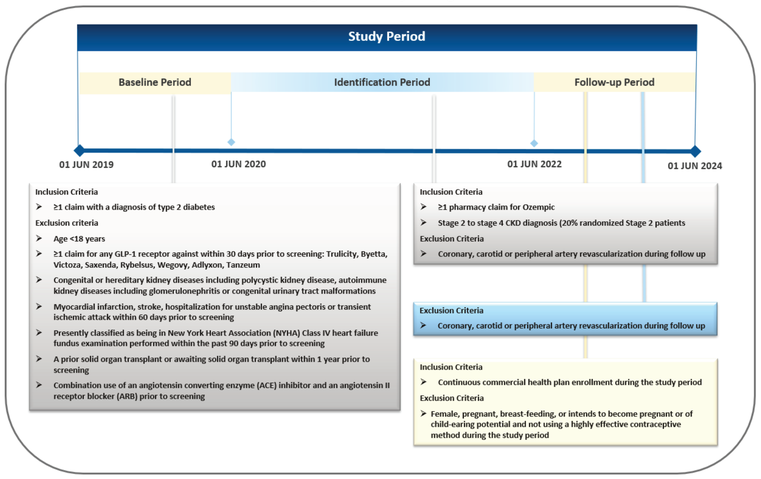
METHODS

Figure 1. Steps in Designing the External Control Arm Study



Using Kythera Labs data from June 2019 to June 2024, an ECA was created based on the inclusion and exclusion criteria identified under the FLOW clinical trial.

Figure 2. Study Design



Primary outcomes were major kidney disease events—a composite of kidney failure onset (dialysis, transplantation, or estimated glomerular filtration rate [eGFR] <15ml/min per 1.73m2), and ≥50% reduction in eGFR from the baseline). Propensity score matching and Cox regression were used to determine risk-adjusted outcomes.

RESULTS

The ECA cohort included 896,257 patients; the clinical trial cohort included 1,766 patients.

Table 1. Study Attrition

	Inclusion Criteria	With Medication
1)	≥1 pharmacy claim for Ozempic during the identification period (01JAN2020 - 01JUN2022); first usage of Ozempic date was assigned as the index date	996,671
2)	≥1 claim with a diagnosis of type 2 diabetes pre index date	431,637
3)	Stage 2 to Stage 4 CKD diagnosis (20% randomized Stage 2 patients)	37,303
4)	Continuous health plan enrollment during the study period	33,976
	Exclusion Criteria	
1)	Age <18 years prior to screening	33,975
2)	≥1 claim with any GLP-1 receptor against within 30 days prior to screening: Trulicity, Byetta, Victoza, Saxenda, Rybelsus, Wegovy, Adlyxon, Tanzeum	32,279
3)	Congenital or hereditary kidney diseases including polycystic kidney disease, autoimmune kidney diseases including glomerulonephritis or congenital urinary tract malformations at baseline	32,209
4)	Myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischemic attack within 60 days prior to screening	30,358
5)	Presently classified as being in New York Heart Association (NYHA) Class IV heart failure at baseline	26,089
6)	Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 90 days prior to screening	25,683
7)	Presence or history of malignant neoplasm within 1 year prior to screening	23,650
8)	A prior solid organ transplant or awaiting solid organ transplant within 1 year prior to screening	23,182
9)	Combination use of an angiotensin converting enzyme (ACE) inhibitor and an angiotensin II receptor blocker (ARB) prior to screening	23,182
10)	Chronic or intermittent haemodialysis or peritoneal dialysis within 90 days after screening	23,169
11)	Coronary, carotid or peripheral artery revascularization during follow-up period	22,908
12)	Female, pregnant, breast-feeding or intends to become pregnant or of child-bearing potential and not using a highly effective contraceptive method during the study period	22,900

	Inclusion Criteria	Without Medication
1)	No Ozempic usage during the study period; a random drug date was assigned during the identification period (01JAN2021 - 01JUL2022)	76,142,839
2)	≥1 claim with a diagnosis of type 2 diabetes pre index date	17,469,058
3)	Stage 2 to Stage 4 CKD diagnosis (20% randomized Stage 2 patients)	1,858,969
4)	Continuous health plan enrollment during the study period	1,305,213
	Exclusion Criteria	
1)	Age <18 years prior to screening	1,305,081
2)	≥1 claim with any GLP-1 receptor against within 30 days prior to screening: Trulicity, Byetta, Victoza, Saxenda, Rybelsus, Wegovy, Adlyxon, Tanzeum	1,297,778
3)	Congenital or hereditary kidney diseases including polycystic kidney disease, autoimmune kidney diseases including glomerulonephritis or congenital urinary tract malformations	1,294,642
4)	Myocardial infarction, stroke, hospitalisation for unstable angina pectoris or transient ischemic attack within 60 days prior to screening	1,213,570
5)	Presently classified as being in New York Heart Association (NYHA) Class IV heart failure	1,040,853
6)	Uncontrolled and potentially unstable diabetic retinopathy or maculopathy. Verified by a fundus examination performed within the past 90 days prior to screening	1,029,915
7)	Presence or history of malignant neoplasm within one year prior to screening	923,417
8)	A prior solid organ transplant or awaiting solid organ transplant within one year prior to screening	906,795
9)	Combination use of an angiotensin converting enzyme (ACE) inhibitor and an angiotensin II receptor blocker (ARB) prior to screening	906,795
10)	Chronic or intermittent haemodialysis or peritoneal dialysis within 90 days after screening	906,155
11)	Coronary, carotid or peripheral artery revascularization during follow-up period	896,497
12)	Female, pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using a highly effective contraceptive method during the study period	896,257

CKD: chronic kidney disease; GLP-1: glucagon-like peptide 1

Table 2. Matched Baseline Characteristics of the Study Cohorts

	With Medication (Ozempic) (N = 17,058)		Without Medication (N = 17,058)		
Characteristics	**N/Mean**	**%/SD**	**N/Mean**	**%/SD**	**p-value**
Age	67.59	9.54	68.94	9.93	0.0000
Age Group: 18-39	120	0.70%	120	0.70%	1.0000
Age Group: 40-59	3032	17.77%	3032	17.77%	1.0000
Age Group: 60-79	12,367	72.50%	12,367	72.50%	1.0000
Age Group: >79	1539	9.02%	1539	9.02%	1.0000
Gender					
Male (%)	7,982	46.79%	7,984	46.81%	0.9878
Female (%)	9,075	53.20%	9,074	53.19%	0.9939
Comorbidity Scores					
Charlson Comorbidity Score (≥ 2)	17,057	100%	17,058	100%	0.4795
Chronic Disease Score (≥ 2)	14,902	87%	7,062	41%	0.0000
Elixhauser Score (≥ 2)	17,058	100%	17,058	100%	0.0000
SES					
Low	6,064	35.55%	5,957	34.92%	0.3912
Medium	5,620	32.95%	5,620	32.95%	1.0000
High	5,148	30.18%	5,148	30.18%	1.0000
Baseline CKD related Comorbidities					
Hypertension	15,935	93.42%	15,801	92.63%	0.0440
Diabetes Mellitus	17,058	100.00%	17,058	100.00%	0.0000
Anemia	1,742	10.21%	1,999	11.72%	0.0016
Mineral and Bone Disorders	1,226	7.19%	1,392	8.16%	0.0170
Depression	3,012	17.66%	2,839	16.64%	0.0789
Sexual Dysfunction	619	3.63%	569	3.34%	0.2964
Calciphylaxis	33	0.19%	34	0.20%	0.9311
Malnutrition	37	0.22%	76	0.45%	0.0094
Rheumatological Diseases	405	2.37%	461	2.70%	0.1729
Inflammatory Bowel Disease	116	0.68%	138	0.81%	0.3272
Chronic Pain	1,781	10.44%	1,584	9.29%	0.0114
Cardiovascular Disease					
Heart Failure	1,389	8.14%	1,444	8.47%	0.4454
Ischemic Heart Disease	4,126	24.19%	3,811	22.34%	0.0043
Peripheral Vascular Disease	1,351	7.92%	1,427	8.37%	0.2874
Any Types of Cardiovascular Disease	5,539	32.47%	5,375	31.51%	0.1783
Mental Health Conditions					
Schizophrenia	83	0.49%	121	0.71%	0.0592
Bipolar Disorder	445	2.61%	380	2.23%	0.1053
Learning Disabilities	29	0.17%	48	0.28%	0.1253
Any Type of Mental Health Condition	517	3.03%	496	2.91%	0.6358

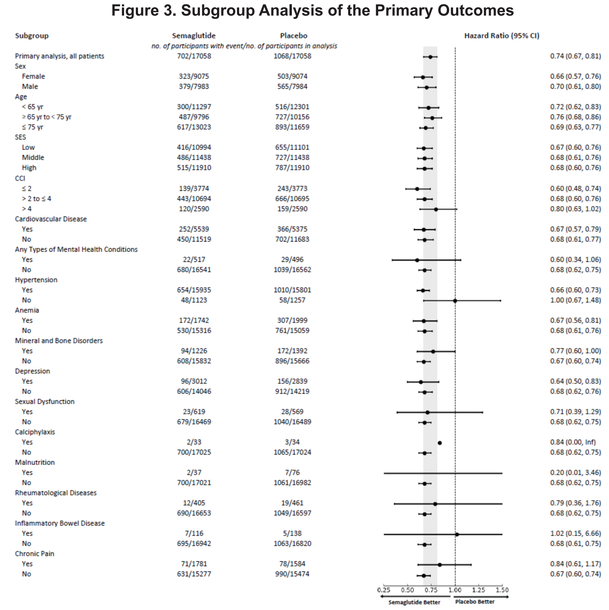
CKD: chronic kidney disease; SD: standard deviation, SES: socioeconomic status

Age, sex, socioeconomic status, and comorbidities (cardiovascular disease, anemia, depression, and mineral and bone disorder) significantly affected the likelihood of a primary event.

After controlling for these factors, primary event risk was 26% lower in the ECA semaglutide group than in the control group (702 vs 1,068 patients; hazard ratio: 0.74; 95% confidence interval: 0.67, 0.81) vs 24% in the clinical trial semaglutide group (**Figure 3**).

RESULTS (cont'd)

Figure 3. Subgroup Analysis of the Primary Outcomes



CCI: Charlson comorbidity index; CI: confidence interval; SES: socioeconomic status

CONCLUSION

Semaglutide treatment demonstrated a significant reduction in the risk of clinically relevant renal outcomes in this real-world ECA study.

Characterized by its expansive sample size, this analysis encompassed a cohort over 500 times larger than that of the corresponding clinical trial. The substantial scale of this real-world evidence provides robust support for the renoprotective effects of semaglutide, reinforcing its potential as a valuable therapeutic option in managing kidney-related complications.

Clinicians can be reassured that the efficacy observed in RCTs is preserved, if not enhanced, in everyday clinical practice; payers and policy makers may consider these data as justification for expanded access and reimbursement. The methodological rigor demonstrated in the construction and analysis of the ECA encompasses data quality assurance, protocol transparency, and robust statistical adjustment, and serves as a model for future studies seeking to leverage real-world data to complement or extend RCT findings.

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145 Hudson St., Suite 205
New York, NY 10013 USA
cdanyc.com

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