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Emulating a Randomized Clinical Trial (TECOS) Using Real-World Data to Assess the Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes

Vanessa Rascon-Velasco [1], Ramzi Argoubi [1], Elise Berliner [2], Martina Furegato [1], Patricia Medina [1]

[1] Oracle Life Sciences, Paris, France, [2] Oracle Life Sciences, Kansas City, MO, USA

Background

- Clinical trial emulation is a methodological approach that uses real-world data (RWD) to replicate the design and analysis of randomized controlled trials (RCTs) in and observational real-world setting. By leveraging large databases such as claims or electronic health records, emulation overcomes the limitations of RCTs, including high costs, ethical concerns, and limited generalizability.
- Advanced statistical methods, such as propensity score matching, help reduce biases and mimic randomization, making it possible to draw more reliable causal conclusions.
- Emulating the TECOS trial, which evaluated the cardiovascular safety of sitagliptin in type 2 diabetes, provides an opportunity to assess whether the results hold in broader, real-world populations.

Objective

We assessed the potential of using a large US claims database to emulate the TECOS - Trial Evaluating Cardiovascular Outcomes with Sitagliptin - clinical trial in a type-2 diabetic population, assessing the effects of adding sitagliptin to usual care on major cardiovascular events (MACE) using second-generation sulfonylureas as proxy for placebo.

Methods

Oracle's US claims collects data from over 160 payers including commercial, Medicare Advantage, and Medicaid data across all 50 states including 150 million patients. Inclusion/exclusion criteria from TECOS were adapted for the population selection and patients were selected between Jan-2015 and 30-Nov-2023. Index date was defined as date of first prescription of sitagliptin or 2G-sulfonylurea.

Patients were excluded if they qualified for both exposure groups. Demographic characteristics were estimated at index-date while baseline covariates related to cardiovascular and diabetes-related complications were determined during the 365 days prior to index date.

The study outcome was defined as having experienced any MACE event (cardiovascular-related death, non-fatal myocardial infarction or non-fatal stroke) during the follow-up period. Propensity score matching (1:1) was performed. Standardized mean differences (SMD) were estimated pre- and post-matching to assess cohort balancing. Kaplan-Meier analysis and Cox proportional hazard model were used to analyze the incidence of MACE events in sitagliptin users (treatment group) or 2G-sulfonylurea users (reference group).

Results

We identified 47,859 patients, of which 13,621 (28.5%) were sitagliptin and 34,238 (71.5%) 2G-sulfonylureas users (**Table 1**). Mean age in the treated group was 63.9(8.6) and 64.1(8.7) in the reference group. 13,614 pairs of exposed and non-exposed patients were identified, who were balanced on 74 baseline covariates (post matching |SMD|≤ 0.1). During the first year of follow-up among matched patients 44.1% of sitagliptin and 44.0% of 2G-sulfonylureas patients experienced a MACE event (p=0.794). For the matched participants, the multivariable-adjusted hazard ratios for having a MACE event related to the use of sitagliptin was 1.00 (95%CI=[0.97 ; 1.04] ; p=0.981) (**Table 3**).

Table 1. Population selection based on adapted inclusion and exclusion criteria from the TECOS trial

Criterion	# Patients
At least 1 Rx of exposure (Sitagliptin) and/or referent (2nd generation sulfonylurea) after 17 Oct 2006	4,319,114
Patients with a confirmed diagnosis of T2DM in the 180 days prior to drug initiation [-180,0]	1,156,186
Patients at least one Rx of either Metformin, pioglitazone, or insulin before drug initiation [-91,0]	556,316
Patient is ≥50 years of age measured on day of drug initiation & no missing gender info [0,0]	401,929
Pre-existing cardiovascular disease: either major coronary artery disease or ischemic cerebrovascular disease [-365,0]	97,875
Exclude patients having a history of type 1 diabetes mellitus or a history of ketoacidosis [-180,0]	88,838
Exclude patients having a history of ≥2 episodes of severe hypoglycemia during the 12 months prior to enrollment [-365,0]	88,678
Exclude patients who have a RX of a DPP-4 inhibitor agent, GLP-1 analogues, or a thiazolidinedione other than pioglitazone within the past 3 months [-91,-1]	80,588
Exclude patients who have a DX of cirrhosis of the liver [-180,0]	80,416
Exclude patients having a diagnosis/procedure code for pregnancy 180 days before index and after index [-180, x]	80,100
Exclude who had a revascularization procedure during the year after index [0, 365]	75,352
Exclude patients qualified in >1 exposure category [0,0]	74,391
Exclude patients with invalid enrollment dates	68,708
Exclude patients with < 180 days of pre-index data	56,398
Exclude patients with < 365 days of pos-tindex data (except in case of death)	50,766
Exclude patients with a combined comorbidity score of >= 10 [-180,0]	47,859
Final population	**47,859**
Sitagliptin	**13,621**
Sulfonylurea	**34,238**

Table 2. Patient characteristics by treatment group

Characteristics		All N=47859	Sitagliptin N=13621	Sulfonylurea N=34238
Age at index	Mean (Sd)	64.01 (8.65)	63.89 (8.64)	64.06 (8.65)
	Q1-Q3	[57.00 ; 70.00]	[57.00 ; 70.00]	[57.00 ; 70.00]
Female	N (%)	20399 (42.62%)	6120 (44.93%)	14279 (41.71%)
Follow-up duration (days)	Mean (Sd)	1579.64 (836.19)	1614.44 (846.92)	1565.79 (831.49)
	Q1-Q3	[848.00 ; 2255.00]	[876.00 ; 2299.00]	[835.00 ; 2234.00]
Race/Ethnicity, N (%)	Unknown	17910 (37.42%)	5033 (36.95%)	12877 (37.61%)
	White	14174 (29.62%)	3993 (29.32%)	10181 (29.74%)
	Hispanic or Latino	6702 (14.00%)	1994 (14.64%)	4708 (13.75%)
	Black or African American	5310 (11.10%)	1566 (11.50%)	3744 (10.94%)
	Other	2432 (5.08%)	615 (4.52%)	1817 (5.31%)
	Asian or Pacific Islander	1331 (2.78%)	420 (3.08%)	911 (2.66%)
Combined comorbidity score	Mean (Sd)	3.37 (2.58)	3.38 (2.58)	3.36 (2.57)
	Q1-Q3	[1.00 ; 5.00]	[1.00 ; 5.00]	[1.00 ; 5.00]
Frailty index, N (%)	Non-frail (<0.15)	5012 (10.47%)	1390 (10.20%)	3622 (10.58%)
	Prefrail (0.15 to <0.25)	30224 (63.15%)	8537 (62.68%)	21687 (63.34%)
	Mildly frail (0.25 to <0.35)	10396 (21.72%)	3006 (22.07%)	7390 (21.58%)
	Moderately frail (0.35 to <0.45)	1918 (4.01%)	581 (4.27%)	1337 (3.91%)
	Severely frail (≥0.45)	309 (0.65%)	107 (0.79%)	202 (0.59%)
Cardiovascular covariates	N (%)	43233 (90.3%)	12176 (89.4%)	31057 (90.7%)
Diabetes-related complications	N (%)	44609 (93.2%)	12598 (92.5%)	32011 (93.5%)
Other covariates, N (%)	Obesity	19660 (41.1%)	5544 (40.7%)	14116 (41.2%)
	Dorsopathies	18405 (38.5%)	5277 (38.7%)	13128 (38.3%)
	Osteoarthritis	14475 (30.3%)	4225 (31.0%)	10250 (29.9%)
	Sleep Disorder	14145 (29.6%)	4117 (30.2%)	10028 (29.3%)
	Depression	13123 (27.4%)	3766 (27.7%)	9357 (27.3%)
	COPD	10839 (22.7%)	3012 (22.1%)	7827 (22.9%)
	Obstructive sleep apnoea	8672 (18.1%)	2560 (18.8%)	6112 (17.9%)
	Smoking	8532 (17.8%)	2328 (17.1%)	6204 (18.1%)
	Hypothyroidism	8444 (17.6%)	2464 (18.1%)	5980 (17.5%)
	Asthma	6109 (12.8%)	1850 (13.6%)	4259 (12.4%)
	Liver disease	5870 (12.3%)	1766 (13.0%)	4104 (12.0%)
	Pneumonia	4724 (9.9%)	1327 (9.7%)	3397 (9.9%)
	Falls	4093 (8.6%)	1267 (9.3%)	2826 (8.3%)
	Drug abuse or dependence	4050 (8.5%)	956 (7.0%)	3094 (9.0%)
	Anxiety disorders	3659 (7.7%)	1037 (7.6%)	2622 (7.7%)
	Fractures	3443 (7.2%)	976 (7.2%)	2467 (7.2%)
	Dementia	2836 (5.9%)	839 (6.2%)	1997 (5.8%)
	Osteoporosis	2414 (5.0%)	733 (5.4%)	1681 (4.9%)
	Alcohol abuse or dependence	2387 (5.0%)	594 (4.4%)	1793 (5.2%)
	Overweight	2341 (4.9%)	699 (5.1%)	1642 (4.8%)
	Other disorders of thyroid gland	1025 (2.1%)	318 (2.3%)	707 (2.1%)
	Hyperthyroidism	636 (1.3%)	193 (1.4%)	443 (1.3%)
	Delirium	305 (0.6%)	77 (0.6%)	228 (0.7%)
	Psychosis	154 (0.3%)	39 (0.3%)	115 (0.3%)

Figure 1. Kaplan-Meier Failure Curves

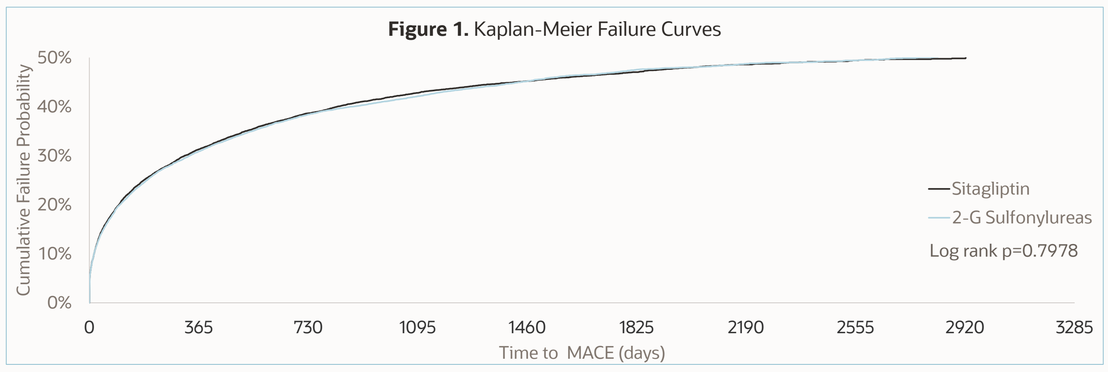

Table 3. Cox model results for MACE with adjusted hazards ratios between treatment groups

	Parameter		Hazard Ratio (95% CI)	p-value		Parameter	Hazard Ratio (95% CI)	p-value
	Treatment group	**Sitagliptin vs. Sulfonylurea**	**1.00 (0.97-1.04)**	**0.981**				
Demographics and clinical	Age at index		1.00 (1.00-1.00)	0.059	Cardiovascular covariates	ACS/unstable angina	0.90 (0.83-0.98)	0.014
	Combined comorbidity score		1.04 (1.03-1.05)	<.0001		Acute MI	1.89 (1.80-1.98)	<.0001
	Gender	Male vs Female	0.95 (0.91-0.99)	0.012		Angina	1.00 (0.93-1.08)	0.960
	Race/Ethnicity vs. White	Asian or Pacific Islander	0.95 (0.86-1.06)	0.380		Atherosclerosis	1.38 (1.32-1.45)	<.0001
		Black or AA	1.12 (1.05-1.19)	0.000		Atrial fibrillation	1.01 (0.96-1.07)	0.638
		Hispanic or Latino	0.99 (0.93-1.05)	0.679		Chronic Ischemic heart disease	1.04 (0.99-1.09)	0.147
		Other	0.88 (0.80-0.96)	0.005		Congestive heart failure	1.08 (1.03-1.13)	0.003
		Unknown	0.83 (0.79-0.87)	<.0001		Hemorrhagic stroke	1.22 (1.06-1.41)	0.005
	Frailty index	Prefrail	1.30 (1.21-1.41)	<.0001		History of CABG or PTCA	0.99 (0.93-1.05)	0.668
	vs. Non-frail	Mildly frail	1.44 (1.31-1.58)	<.0001		Ischemic stroke (w and w/o mention of cerebral infarction)	2.89 (2.74-3.05)	<.0001
		Moderately frail	1.61 (1.42-1.83)	<.0001		Old MI	2.48 (2.37-2.59)	<.0001
		Severely frail	1.59 (1.29-1.96)	<.0001		Other cardiac dysrhythmia/ cardiac arrhythmias	0.91 (0.87-0.96)	0.000
	Index year	2016	0.69 (0.62-0.76)	<.0001		Other cerebrovascular disease	1.12 (1.07-1.17)	<.0001
	vs. 2015	2017	0.66 (0.59-0.73)	<.0001		Other forms of chronic ischemic heart disease	1.05 (0.97-1.14)	0.235
		2018	0.62 (0.56-0.69)	<.0001		Peripheral vascular disorders	0.86 (0.82-0.90)	<.0001
		2019	0.58 (0.52-0.64)	<.0001		Stable angina	1.02 (0.93-1.13)	0.688
		2020	0.60 (0.54-0.67)	<.0001		Subsequent MI	1.47 (1.12-1.92)	0.005
		2021	0.65 (0.58-0.72)	<.0001		Transient ischemic attack (TIA)	1.00 (0.93-1.07)	0.992
		2022	0.55 (0.49-0.61)	<.0001				
		2023	1.08 (0.62-1.88)	0.788				
Diabetes-related complications	Bladder stones		0.97 (0.72-1.31)	0.858	Other covariates	Alcohol abuse or dependence	0.99 (0.90-1.08)	0.791
	Cellulitis or abscess of toe		1.13 (1.02-1.25)	0.023		Anxiety disorders	0.97 (0.91-1.05)	0.482
	Chronic kidney disease/Occurrence of chronic renal insufficiency		0.96 (0.90-1.02)	0.167		Asthma	0.95 (0.90-1.01)	0.099
	Cystology		1.00 (0.87-1.15)	0.953		COPD	1.02 (0.97-1.07)	0.415
	Diabetes mellitus without mention of complications		0.84 (0.79-0.91)	<.0001		Delirium	1.01 (0.82-1.25)	0.912
	Diabetes with other ophthalmic manifestations		1.06 (1.01-1.11)	0.024		Dementia	1.05 (0.97-1.14)	0.198
	Diabetes with peripheral circulatory disorders		1.01 (0.97-1.06)	0.611		Depression	0.95 (0.91-1.00)	0.040
	Diabetes with unspecified complication		0.99 (0.94-1.03)	0.548		Dorsopathies	0.96 (0.92-1.00)	0.043
	Disorders of fluid electrolyte and acid-base balance		0.94 (0.90-0.99)	0.017		Drug abuse or dependence	1.05 (0.97-1.12)	0.220
	Edema		0.98 (0.93-1.03)	0.379		Falls	1.05 (0.98-1.12)	0.163
	Erectile dysfunction		0.84 (0.64-1.12)	0.230		Fractures	0.99 (0.92-1.07)	0.823
	Foot ulcer		0.97 (0.89-1.05)	0.426		Hyperthyroidism	0.81 (0.69-0.95)	0.011
	Glaucoma		0.96 (0.90-1.02)	0.204		Hypothyroidism	0.94 (0.90-0.99)	0.027
	Hyperosmolar hyperglycemic nonketotic syndrome (HONK)		1.06 (0.94-1.18)	0.349		Liver disease	0.93 (0.88-0.99)	0.015
	Hyperglycemia		1.03 (0.99-1.07)	0.176		Obesity	0.97 (0.93-1.01)	0.160
	Hyperlipidemia		0.99 (0.93-1.06)	0.840		Obstructive sleep apnea	0.99 (0.92-1.06)	0.715
	Hypertension		0.95 (0.87-1.04)	0.265		Osteoarthritis	0.95 (0.91-1.00)	0.031
	Hypertensive nephropathy		1.01 (0.94-1.08)	0.861		Osteoporosis	0.99 (0.91-1.08)	0.883
	Hypoglycemia		1.02 (0.95-1.10)	0.555		Other disorders of thyroid gland	0.96 (0.85-1.09)	0.551
	Kidney stones		1.04 (0.96-1.12)	0.397		Overweight	0.95 (0.87-1.04)	0.262
	Occurrence of acute renal disease		1.02 (0.96-1.08)	0.540		Pneumonia	0.95 (0.90-1.01)	0.125
	Osteomyelitis		0.82 (0.73-0.92)	0.001		Psychosis	1.12 (0.82-1.52)	0.470
	Renal Dysfunction (non-diabetic)		1.03 (0.95-1.12)	0.431		Sleep Disorder	0.97 (0.92-1.03)	0.365
	Retinal detachment, vitreous hemorrhage, vitrectomy		0.94 (0.82-1.07)	0.343		Smoking	1.11 (1.05-1.16)	0.000
	Skin infections		0.96 (0.92-1.01)	0.098				
	Urinary tract infections (UTIs)		1.04 (0.99-1.09)	0.113				

Conclusion

This study found no significant differences in cardiovascular risk between sitagliptin and second-generation sulfonylureas, aligning with the findings of the TECOS trial and demonstrating the potential of real-world evidence to inform drug development and regulatory decisions.

This secondary claims database study could be further enhanced by linkage with electronic health records (EHR), for more precise population identification through laboratory results, improved capture of outcomes and a better matching accuracy.

References

1. Franklin JM, Patorno E, Desai RJ, et al. Emulating Randomized Clinical Trials With Nonrandomized Real-World Evidence Studies: First Results From the RCT DUPLICATE Initiative. *Circulation*. 2021;143(10):1002-1013. doi:10.1161/CIRCULATIONAHA.120.051718
2. Green JB, Bethel MA, Armstrong PW, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2015;373(3):232-242. doi:10.1056/NEJMoa1501352
3. Green JB, Bethel MA, Paul SK, et al. Rationale, design, and organization of a randomized, controlled Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) in patients with type 2 diabetes and established cardiovascular disease. *American Heart Journal*. 2013;166(6):983-989.e7. doi:10.1016/j.ahj.2013.09.003

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