

LOWER RISK OF CARDIOVASCULAR EVENTS AND DEATH ASSOCIATED WITH INITIATION OF SGLT-2 INHIBITORS VERSUS OTHER GLUCOSE LOWERING DRUGS - REAL WORLD DATA ACROSS THREE MAJOR WORLD REGIONS WITH MORE THAN 400,000 PATIENTS: THE CVD-REAL 2 STUDY

Mikhail Kosiborod, MD on behalf of the CVD-REAL Investigators and Study Group



Lower Risk of Cardiovascular Events and Death Associated with Initiation of SGLT-2 Inhibitors versus Other Glucose Lowering Drugs - Real World Data Across Three Major World Regions with More Than 400,000 Patients: The CVD-REAL 2 Study

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- Outcomes trials demonstrated lower risks of cardiovascular events with sodium glucose cotransporter-2 inhibitors (SGLT-2i) in patients with type 2 diabetes (T2D), most with established cardiovascular disease (CVD)^{1,2}
- CVD-REAL a large, international pharmaco-epidemiologic study demonstrated that SGLT-2i were associated with similar CV effects across compounds, and in a much broader population of patients with T2D seen in clinical practice³
 - However, those analyses focused on all-cause death (ACD) and heart failure, and only included patients from the United States and Europe





- Most patients with T2D reside outside the US and Europe (primarily in Asia-Pacific and the Middle East)¹
- There are important differences in patient characteristics, treatment patterns, and types
 of adverse CVD events experienced by patients in these world regions (e.g. stroke being
 much more common in Asia²)
- Data from large, well-designed comparative effectiveness studies evaluating CV outcomes with various T2D therapies has been limited outside the US and Europe

1. International Diabetes Federation. IDF Diabetes Atlas: 8th edition, 2017; 2. Ueshima H, et al. Circulation 2008;118:2702-9.







 To evaluate the relationship between the initiation of SGLT-2i vs. other glucose-lowering drugs (oGLD) and a broad range of CV outcomes (allcause death, HHF, MI and stroke) in patients with T2D from three major world regions: Asia-Pacific, Middle East, and North America

Countries and Data Sources





Australia – National Diabetes Services Scheme (NDSS)*



Canada – Manitoba Population Health Research Data Repository



Israel – The Maccabi Health Management Organization



Japan – Medical Data Vision



Singapore – SingHealth Diabetes Registry



South Korea – National Health Insurance Service (NHIS)



^{*}Included in the ACD analysis only

Inclusion/Exclusion Criteria



- Inclusion
 - New users of SGLT-2i or oGLD
 - Established type 2 diabetes on or prior to the index date
 - ≥18 years old
 - >1 year historical data available prior to the index date
- Exclusion
 - Patients with type 1 diabetes or gestational diabetes



Outcomes



- All-cause death
- Hospitalization for heart failure (HHF)
- All-cause death or HHF
- Myocardial infarction (MI)
- Stroke





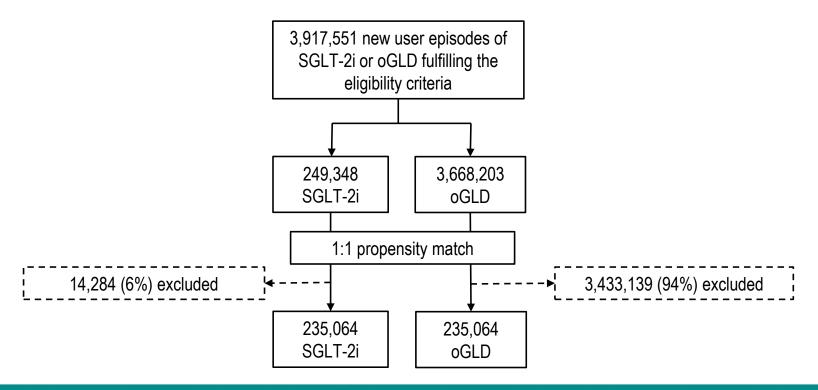


- All episodes of initiation of an SGLT-2i or oGLD were eligible for inclusion
- Propensity score for initiating SGLT-2i was developed, and episodes of SGLT-2i and oGLD initiation were matched 1:1 in each country
- Cox proportional hazards models were used for each outcome
- Hazard ratios for each country were pooled for an overall summary estimate
- Primary analysis was intent-to-treat (ITT) follow up regardless of whether the index treatment was discontinued
- Multiple subgroup and sensitivity analyses used to evaluate stability of findings



Patient Population









Baseline Characteristics

Baseline characteristic, n (%)	SGLT-2i (N=235,064)	oGLD (N=235,064)	Standardized Difference	
Age, years, mean (SD)	57 (12)	57 (13)	0.4%	
Women	105,843 (45)	106,863 (46)	0.9%	
Established cardiovascular disease*	59,222 (27)	56,576 (26)	2.7%	
Acute myocardial infarction	7,624 (3)	7,479 (3)	0.4%	
Unstable angina	12,480 (6)	12,235 (6)	0.5%	
Heart failure	15,151 (7)	14,741 (7)	0.7%	
Atrial fibrillation	6,026 (3)	5,843 (3)	0.5%	
Stroke	20,983 (10)	20,153 (9)	1.3%	
Peripheral arterial disease	2,446 (1)	2,384 (1)	0.3%	
Microvascular disease†	116,370 (53)	114,630 (52)	1.6%	
Chronic kidney disease	4,211 (2)	4,021 (2)	0.6%	

^{*}Myocardial infarction, unstable angina, stroke, heart failure, transient ischemic attack, coronary revascularization or occlusive peripheral artery disease; †diabetic mono-/polyneuropathy, diabetic eye complications, diabetic foot/peripheral angiopathy, or diabetic kidney disease





Baseline Therapies

Baseline therapies, n (%)	SGLT-2i (N=235,064)	oGLD (N=235,064)	Standardized Difference
Cardiovascular thera	apies		
Antihypertensive therapy [†]	147,166 (63)	145,014 (62)	1.9%
Loop diuretics	16,451 (7)	16,100 (9)	0.6%
Thiazides	17,608 (8)	17,173 (7)	0.7%
ACE inhibitors	20,199 (9)	20,062 (9)	0.2%
ARBs	109,620 (47)	109,347 (47)	0.2%
Statins	153,694 (65)	153,466 (65)	0.2%
Beta-blockers	44,786 (19)	43,947 (19)	0.9%
Aldosterone antagonists	6,719 (3)	6,548 (3)	0.4%

 † Includes angiotensin converting enzyme inhibitors, angiotensin receptor blockers, Ca2+ channel blockers, β -blockers, thiazides; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers

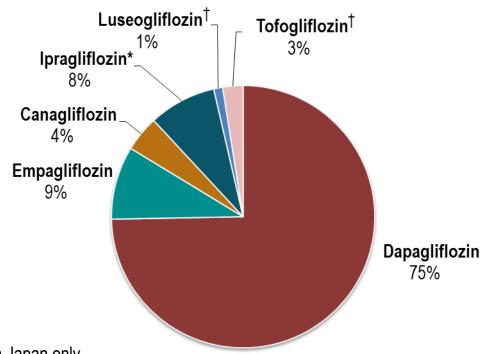
Baseline therapies, n (%)	SGLT-2i oGLD (N=235,064) (N=235,064)		Standardized Difference	
Glucose-lowering the	erapies			
Metformin	173,783 (74)	175,266 (75)	1.4%	
Sufonylurea	121,209 (52) 119,466 (51)		1.5%	
DPP-4 inhibitor	130,674 (56) 128,096 (55)		2.2%	
Thiazolidinedione	30,503 (13)	29,573 (13)	1.2%	
GLP-1 receptor agonist	6,163 (3)	6,022 (3)	0.4%	
Insulin	46,486 (20)	44,480 (19)	2.2%	

DPP-4, Dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1





Use of SGLT-2i: Proportion of Exposure Time



*In South Korea and Japan; †In Japan only.



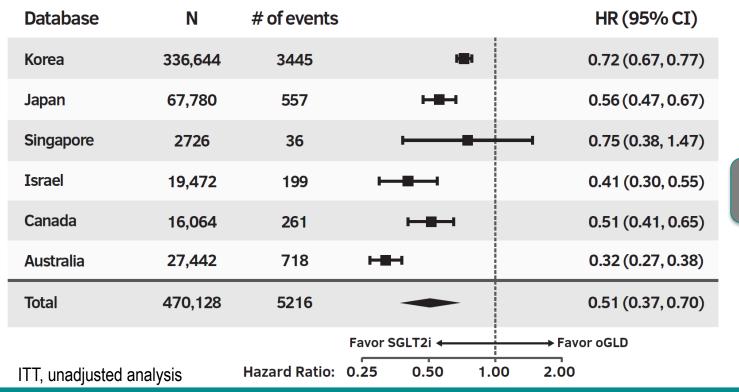


RESULTS



All-Cause Death





P-value for SGLT2i vs. oGLD: p<0.001

Heterogeneity p-value: p<0.001



Hospitalization for Heart Failure



Database	N	# of events		HR (95% CI)
Korea	336,644	5149	1984	0.87 (0.82, 0.92)
Japan	67,780	565	⊢⊞ -1	0.75 (0.63, 0.89)
Singapore	2726	67		0.62 (0.38, 1.02)
Israel	19,472	128	⊢= →	0.53 (0.37, 0.75)
Canada	16,064	88		0.36 (0.24, 0.56)
Total	442,686	5997	-	0.64 (0.50, 0.82)
			Favor SGLT2i ←	→ Favor oGLD
ITT, unadjusted an	nalysis	Hazard Ratio:	0.25 0.50 1.00	2.00

P-value for SGLT2i vs. oGLD: p<0.001

Heterogeneity p-value: p<0.001



Composite of All-Cause Death or HHF



Database	N	# of events		HR (95% CI)	
Korea	336,644	7990	•	0.81 (0.78, 0.85)	
Japan	67,780	1061	HBH	0.65 (0.57, 0.74)	
Singapore	2726	93	⊢= →	0.62 (0.41, 0.95)	
Israel	19,472	313	⊢= →	0.45 (0.36, 0.57)	
Canada	16,064	331	⊢= ⊣	0.48 (0.39, 0.59)	
Total	442,686	9788	•	0.60 (0.47, 0.76)	
			Favor SGLT2i ←	Favor oGLD	
ITT, unadjusted a	nalysis	Hazard Ratio:	0.25 0.50 1.00	2.00	

P-value for SGLT2i vs. oGLD: p<0.001

Heterogeneity p-value: p<0.001



Myocardial Infarction



Database	N	# of events		HR (95% CI)
Korea	336,644	1901	HEH	0.81 (0.74, 0.89)
Japan	67,780	91	ı— =	0.75 (0.50, 1.14)
Singapore	2726	70	· · · · · · · · · · · · · · · · · · ·	0.79 (0.49, 1.27)
Israel	19,472	59	ı <u> </u>	1.09 (0.66, 1.80)
Canada	16,064	128		0.75 (0.56, 1.01)
Total	442,686	2249	*	0.81 (0.74, 0.88)
			Favor SGLT2i ← → Fa	avor oGLD
ITT, unadjusted a	nalysis	Hazard Ratio:	0.25 0.50 1.00 2.0	0

P-value for SGLT2i vs. oGLD: p<0.001

Heterogeneity p-value: p=0.787



Stroke



Database	N	# of events		HR (95% CI)	
Korea	336,644	5972	•	0.82 (0.78, 0.86)	
Japan	67,780	272	⊢= →	0.66 (0.52, 0.84)	
Singapore	2726	34	←■	0.34 (0.15, 0.75)	P-value for
Israel	19,472	116	⊢=	0.66 (0.47, 0.94)	SGLT2i vs. oGLD: p<0.001
Canada	16,064	45		0.55 (0.32, 0.94)	
Total	442,686	6439	-	0.68 (0.55, 0.84)	
			Favor SGLT2i ←	→ Favor oGLD	
ITT, unadjusted a	nalysis	Hazard Ratio:	0.25 0.50 1.00	2.00	Heterogeneity p-value: p=0.029



Subgroup Analyses – Outcomes With and Without CVD at Baseline



Event		Event rate	HR (95% CI)	P-value interaction
All-cause death	Prior CVD No Prior CVD	1.98 0.70	H≣+1 ■1	0.198
Heart Failure	Prior CVD No Prior CVD	3.73 0.60	⊢= ⊢	0.738
HHF or ACD	Prior CVD No Prior CVD	5.31 1.23	HB-1	0.303
MI	Prior CVD No Prior CVD	1.15 0.30	HBH HBH	0.595
Stroke	Prior CVD No Prior CVD	3.73 0.74	 	0.299
		Hazard Ratio:	Favor SGLT2i	Favor oGLD





Limitations



- Possibility of residual, unmeasured confounding cannot be definitively excluded
- Mortality data were available only from inpatient settings in Japan and Singapore
 - However, most fatal events in these countries occur in the hospital
 - Sensitivity analyses excluding data from Japan and Singapore produced similar results
- Did not examine safety
- SGLT-2i experience in real-world practice is still relatively short
 - Longer-term follow up required to examine whether effects are sustained over time







- Large, international study across three major world regions, over 400,000 patients and large number of events for each outcome
- Initiation of SGLT-2i vs. oGLDs associated with lower risk of death, HHF, MI and stroke
 - Directionality of associations generally consistent across countries
 - Results stable in multiple sensitivity analyses and across patient subgroups
- Findings suggest that CV effects of SGLT-2i may extend across patient ethnic and racial backgrounds, geographic regions, as well as CV risk continuum





Manuscript now published in JACC

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CVDREAL²

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