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66th Annual Scientific Session & Expo

LOWER RATES OF HOSPITALIZATION FOR HEART FAILURE AND ALL-CAUSE DEATH IN NEW USERS OF SGLT-2 INHIBITORS VERSUS OTHER GLUCOSE LOWERING DRUGS – REAL WORLD DATA FROM SIX COUNTRIES AND MORE THAN 300,000 PATIENTS: THE CVD-REAL STUDY

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

WASHINGTON, DC
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Lower Rates of Hospitalization for Heart Failure and All-Cause Death in New Users of SGLT-2 Inhibitors: The CVD-REAL Study

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Background

- Patients with Type 2 diabetes (T2D) are at high risk for developing cardiovascular disease (CVD) complications, including heart failure

- The EMPA-REG OUTCOME trial demonstrated a reduction in hospitalization for heart failure (HHF) and all-cause death with the sodium-glucose co-transporter-2 (SGLT-2) inhibitor, empagliflozin, in patients with Type 2 diabetes and established cardiovascular disease[1]

Zinman B et al. *N Engl J Med*. 2015;26:2117–28

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Key Unanswered Questions

- Are the observed benefits compound-specific, or do they represent a “class effect”?
- Will effects observed in those with established cardiovascular disease apply to a Type 2 diabetes population with a broader cardiovascular risk profile?
- Will the effects observed in EMPA-REG OUTCOME translate to real world clinical practice?

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Study Objectives

Primary

- Compare risk of HHF in patients with Type 2 diabetes newly initiated on SGLT-2 inhibitors versus other glucose-lowering drugs (GLDs)

Secondary

- Compare risk of all-cause death between the two treatment groups
- Compare risk of HHF or all-cause death between the two treatment groups

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Data Sources: Health Records Across Six Countries


Truven MarketScan Claims & Encounters and linked Medicare


National full-population registries


National full-population registries


National full-population registries


Clinical Practice Research Datalink (CPRD) and
The Health Improvement Network (THIN)


Diabetes Patienten Verlaufsdokumentation (DPV) initiative

Cohort 1
HHF

Cohort 2
All-cause death
and composite
HHF/all-cause death

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Inclusion/Exclusion Criteria

Inclusion

- New users receiving SGLT-2 inhibitors or other GLDs
  - 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
- Patients with gestational diabetes

*In Germany, >6 months

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Statistical Analysis

- Non-parsimonious propensity score developed for '*being initiated on an SGLT-2 inhibitor*' within each country to minimize confounding by indication
- Patients in SGLT-2 inhibitor and other GLD groups matched 1:1 by propensity score
- Incidence rates for HHF, all-cause death, and the composite endpoint of HHF/all-cause death calculated separately within each country
- Hazard ratios and 95% CI for all outcomes derived for SGLT-2 inhibitor versus other GLD treatment groups within each country using Cox proportional hazards models
- Time-to-first event used for all outcomes

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Statistical Analysis (Continued)

- A meta-analysis approach used[1]
  - Hazard ratios from each country pooled to obtain summary weighted point estimates with 95% CI
- Primary analyses for all three endpoints used an on-treatment, unadjusted approach
- Sensitivity analyses assessed stability of estimates:
  - Multivariable adjustment
  - Intent-to-Treat (ITT)
  - Step-wise removal of thiazolidinedione (TZD), insulin, sulfonylurea (SU) from control group

[1]DerSimonian R & Laird N. *Controlled clinical trials.* 1986;7:177–88

RESULTS

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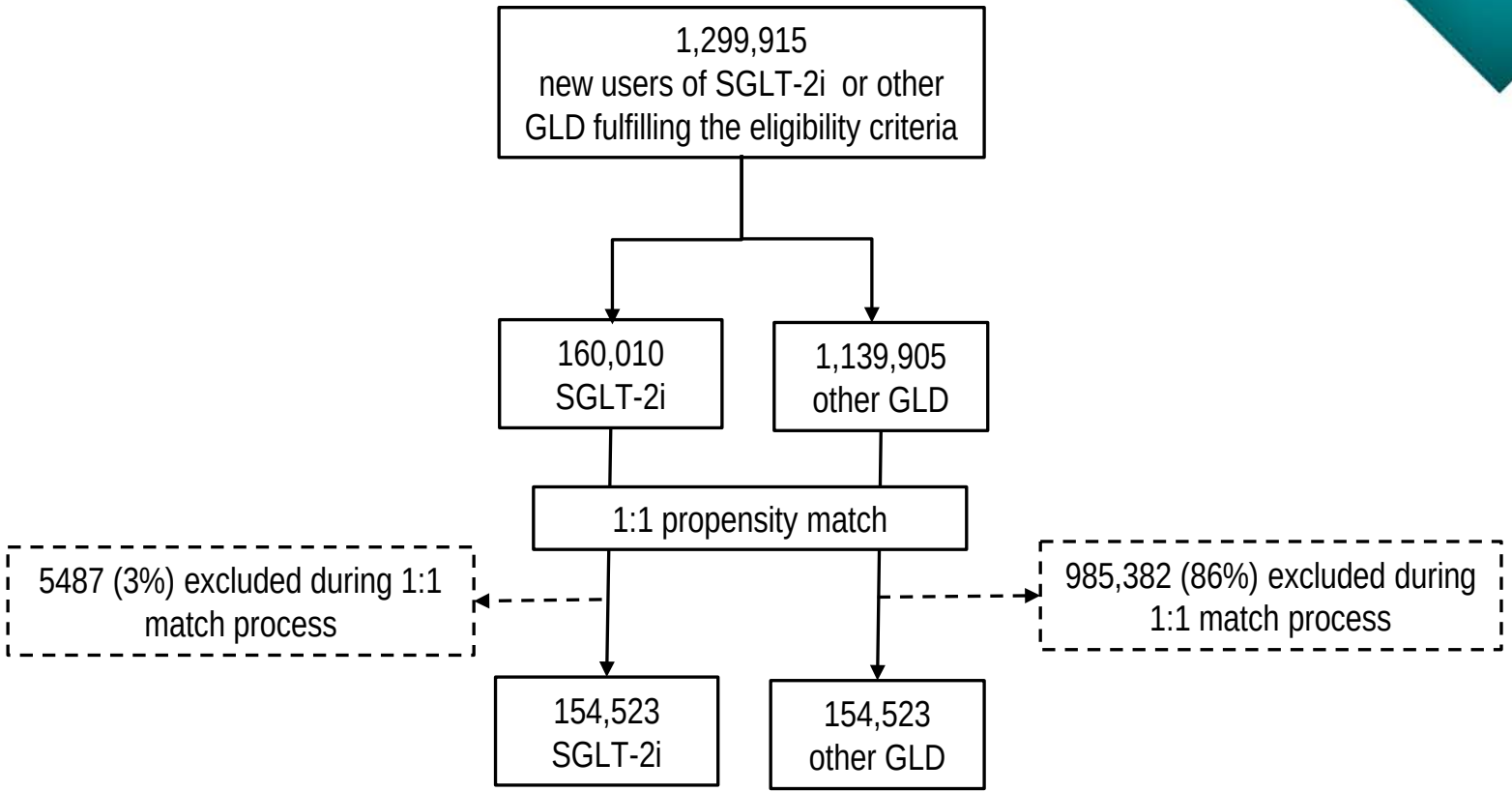
Patient Population



SGLT-2i=sodium-glucose co-transporter-2 inhibitor

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Baseline Characteristics for Propensity Match Cohort

	SGLT-2 inhibitor* N=154,523	Other GLD* N=154,523
Age, years, mean (SD)	57.0 (9.9)	57.0 (10.1)
Women	68,419 (44.3)	68,770 (44.5)
Established cardiovascular disease†	20,043 (13.0)	20,302 (13.1)
Acute myocardial infarction	3792 (2.5)	3882 (2.5)
Unstable angina	2529 (1.6)	2568 (1.7)
Heart failure	4714 (3.1)	4759 (3.1)
Atrial fibrillation	5632 (3.6)	5698 (3.7)
Stroke	6347 (4.1)	6394 (4.1)
Peripheral arterial disease	5239 (3.4)	5229 (3.4)
Microvascular disease	42,214 (27.3)	42,221 (27.3)
Chronic kidney disease	3920 (2.5)	4170 (2.7)

*Data are n (%) unless otherwise stated; †Myocardial infarction, unstable angina, stroke, heart failure, transient ischemic attack, coronary revascularization or occlusive peripheral artery disease

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Baseline Characteristics for Propensity Match Cohort

	SGLT-2 inhibitor* N=154,523	Other GLD* N=154,523
Cardiovascular therapies		
Antihypertensive therapy†	123,691 (80.0)	123,560 (80.0)
Loop diuretics	14,280 (9.2)	14,314 (9.3)
Thiazides	42,444 (27.5)	42,509 (27.5)
ACE inhibitors	66,812 (43.2)	67,067 (43.4)
ARBs	48,718 (31.5)	48,443 (31.4)
Statins	103,966 (67.3)	104,126 (67.4)
Diabetes therapies		
Metformin	121,496 (78.6)	123,429 (79.9)
Sufonylurea	59,405 (38.4)	59,786 (38.7)
DPP-4 inhibitor	51,398 (33.3)	50,088 (32.4)
Thiazolidinedione	13,649 (8.8)	12,970 (8.4)
GLP-1 receptor agonist	31,352 (20.3)	27,086 (17.5)
Insulin	45,570 (29.5)	45,095 (29.2)

*Data are n (%); †Includes angiotensin converting enzyme inhibitors, angiotensin receptor blockers, Ca2+ channel blockers, β-blockers, thiazides; ACEi=angiotensin-converting-enzyme; ARB=angiotensin II receptor blockers; DPP-4=Dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1

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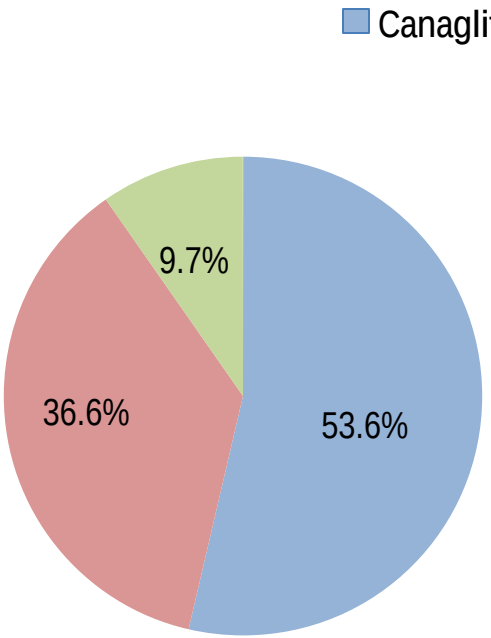
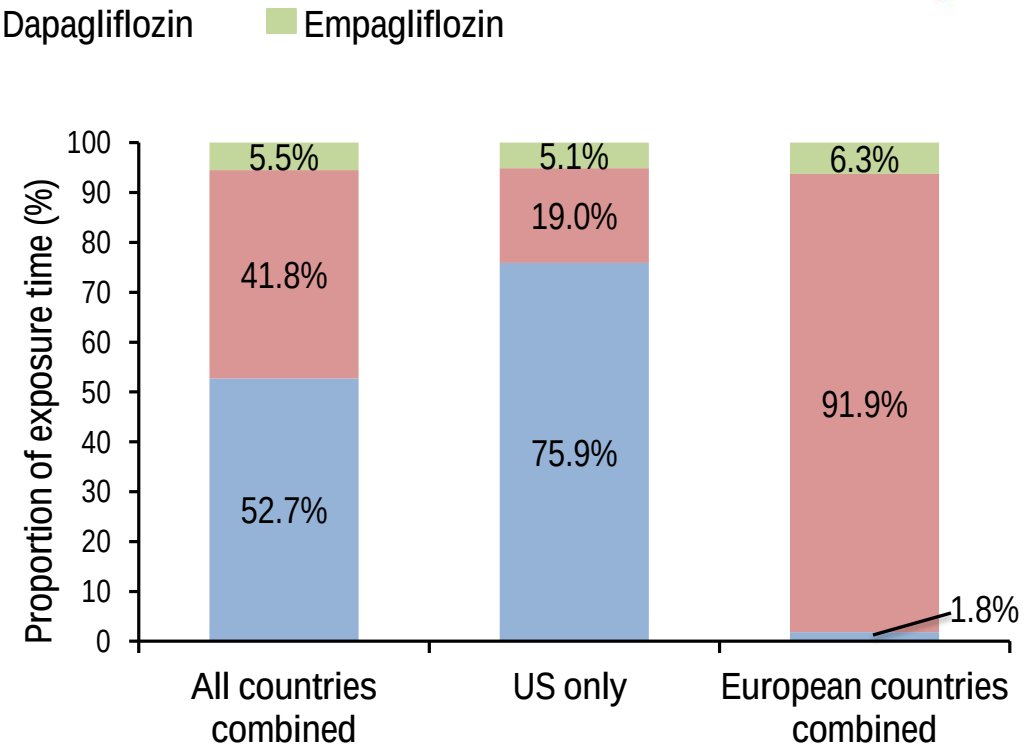
Contribution of SGLT-2 inhibitor Class as a Proportion of Exposure Time in Propensity-Match Cohorts

Cohort 1: HHF Analysis (N=309,046)





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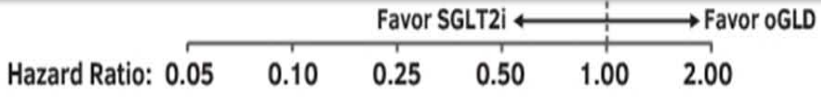
HHF Primary Analysis

Database	N	# of events	HR (95% CI)
US	233,798	298	0.55 (0.44, 0.69)
Norway	25,050	278	0.62 (0.49, 0.79)
Denmark	18,468	167	0.77 (0.59, 1.01)
Sweden	18,378	191	0.61 (0.45, 0.82)
UK	10,462	16	0.36 (0.12, 1.13)
Germany	2900	11	0.14 (0.03, 0.68)
Total	309,056	961	0.61 (0.51, 0.73)



P-value for SGLT2i vs oGLD: <0.001

Heterogeneity p-value: 0.169

Data are on treatment, unadjusted; oGLD=other glucose-lowering drug; HR=hazard ratio

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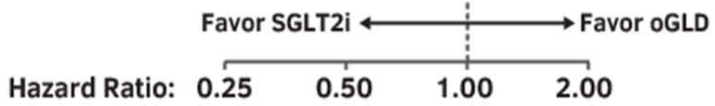
Sensitivity Analyses: HHF (Pooled Estimates)

Outcome	N	# of events	HR (95% CI)
On treatment, adjusted*	309,056	961	0.61 (0.53, 0.69)
ITT, unadjusted	309,056	1379	0.67 (0.60, 0.75)
On treatment, adjusted*, excluding TZD, insulin and SU	196,802	423	0.57 (0.42, 0.76)



For all analyses, P-value for SGLT2i vs oGLD: <0.001

Includes data for US, Norway, Denmark, Sweden only; *Adjusted for previous heart failure, age, gender, frailty, previous myocardial infarction, previous atrial fibrillation, hypertension, obesity / body mass index, duration of diabetes, ACE inhibitor or ARB use; β-blocker or α-blocker use, Ca^{+}-channel blocker use, loop diuretic use, thiazide diuretic use

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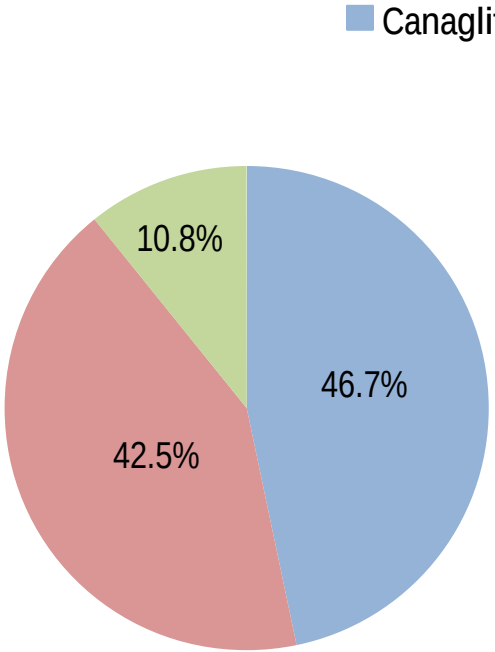
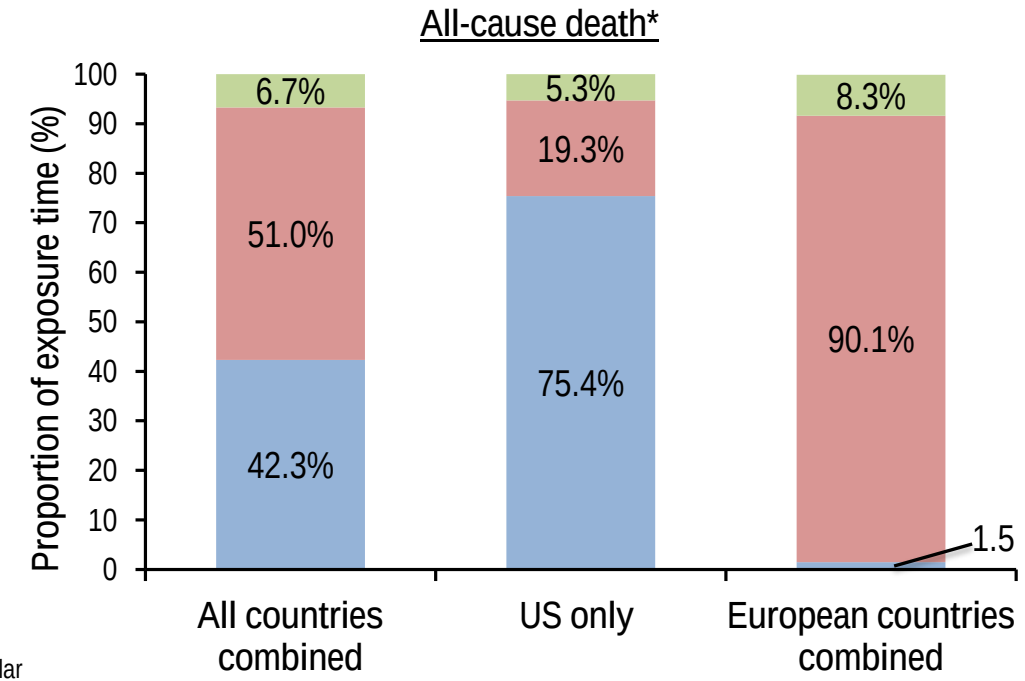
Contribution of SGLT-2 inhibitor Class as a Proportion of Exposure Time in Propensity-Match Cohorts

Cohort 2: All-Cause Death and HHF or All-Cause Death Analyses (N=215,622)





*Data shown are for all-cause death; data for HHF or all-cause death are similar

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All-Cause Death Primary Analysis

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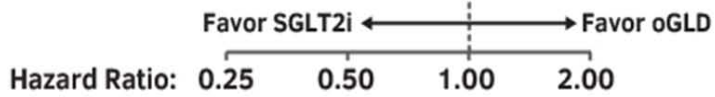
Database	N	# of events	HR (95% CI)
US	143,264	250	0.38 (0.29, 0.50)
Norway	25,050	364	0.55 (0.44, 0.68)
Denmark	18,468	323	0.46 (0.37, 0.57)
Sweden	18,378	317	0.47 (0.37, 0.60)
UK	10,462	80	0.73 (0.47, 1.15)
Total	215,622	1334	0.49 (0.41, 0.57)



P-value for SGLT2i vs oGLD: <0.001

Heterogeneity p-value: 0.089

Data are on treatment, unadjusted; oGLD=other glucose-lowering drug; HR=hazard ratio

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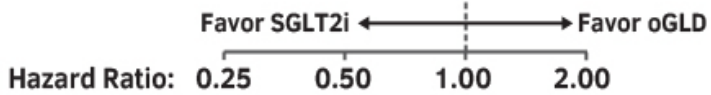
HHF or All-Cause Death Primary Analysis

Database	N	# of events	HR (95% CI)
US	143,264	424	0.44 (0.36, 0.54)
Norway	25,050	622	0.58 (0.50, 0.69)
Denmark	18,468	477	0.57 (0.48, 0.67)
Sweden	18,378	364	0.50 (0.41, 0.63)
UK	10,462	96	0.66 (0.44, 1.00)
Total	215,622	1983	0.54 (0.48, 0.60)



P-value for SGLT2i vs oGLD: <0.001

Heterogeneity p-value: 0.166

Data are on treatment, unadjusted; oGLD=other glucose-lowering drug; HR=hazard ratio

Limitations

- Possibility of residual, unmeasured confounding cannot be definitively excluded
  - However, results were similar across countries, and remarkably stable in multiple sensitivity analyses
- Did not examine other cardiovascular events, such as myocardial infarction and stroke
  - However, HHF is arguably the most common and morbid cardiovascular complication in Type 2 diabetes
- Adjudication of events was not possible (de-identified data and large cohorts)
- Did not focus on safety
- SGLT-2 inhibitor experience in real-world practice is still relatively short
  - Longer-term follow up required to examine whether effects are sustained over time

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Conclusions

- In a large real-world study across six countries and a broad population of patients with Type 2 diabetes, treatment with SGLT-2 inhibitors versus other GLDs was associated with significant reductions in:
  - Hospitalization for heart failure
  - All-cause death
  - Hospitalization for heart failure or all-cause death

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Clinical Implications

- No significant heterogeneity across countries, despite geographic variations in use of SGLT-2 inhibitors (predominance of canagliflozin in US and dapagliflozin in other countries)
  - The observed cardiovascular benefits are likely class-related
- Broad population of patients with Type 2 diabetes in general practice, the overwhelming majority (87%) of whom did not have known cardiovascular disease
  - Benefits may extend to those at the lower end of the risk spectrum
- HHF and death analyses similar to those seen in EMPA-REG OUTCOME
  - Benefits appear to translate to real-world clinical practice

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