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Empagliflozin on the risk of retinopathy in patients with type 2 diabetes: Results from the EMPRISE study

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Disclosures

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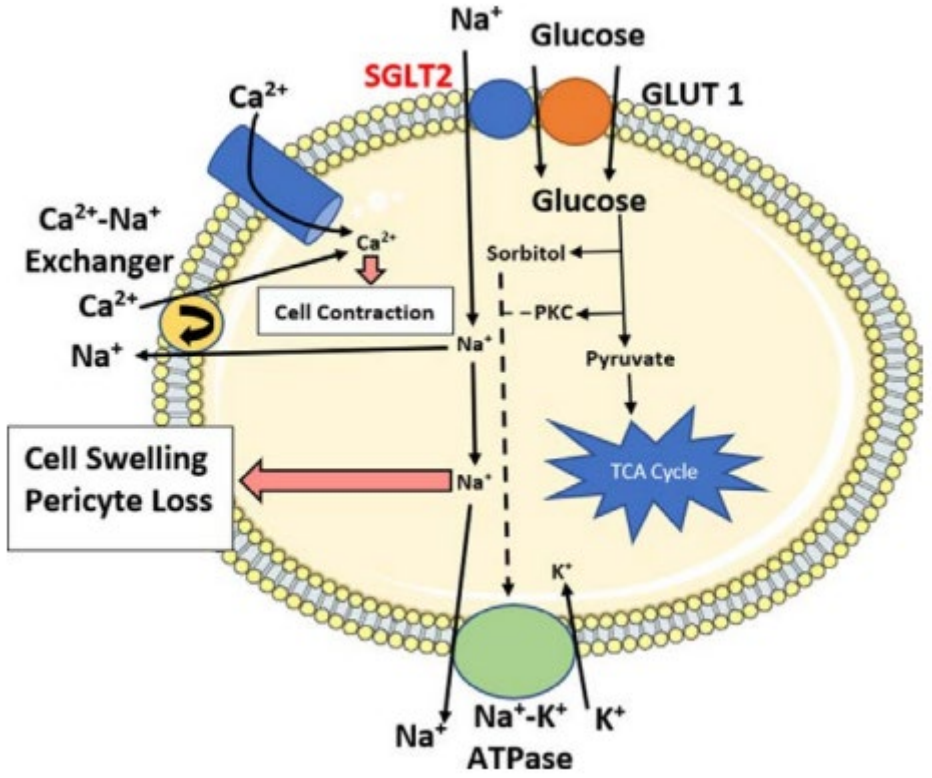
Background

- Diabetic retinopathy (DR) affects one third of adults with diabetes. It is the leading cause of blindness among working age adults and is projected to affect 16 million people with diabetes in the US by 2050.[1,2]
- Empagliflozin, a sodium-glucose cotransporter-2 inhibitor (SGLT-2i), has demonstrated many cardiovascular and renal benefits for patients with type 2 diabetes (T2D) in large cardiovascular outcome trials.
- However, the role of empagliflozin and other SGLT-2is with respect to DR is not completely understood.

1. Harding et al. Diabetologia 2019; 2. CDC. 2021

SGLT2i and DR

- There are multiple proposed mechanisms through which SGLT-2i may reduce DR:
  - ↓ damage to retina microvasculature
  - ↓ pericyte loss
  - Vascular endothelial growth factor (VEGF) modulation



1. Lahoti et al. Cardiovascular Endocrinology & Metabolism. 2021.

SGLT2i and DR – evidence from RCTs

- In a post-hoc analysis of the EMPA-REG OUTCOME trial, compared with placebo, empagliflozin reduced the risk of retinopathy (composite of initiation retinal photocoagulation, vitreous hemorrhage, diabetes-related blindness, or initiation of intravitreal injections) by 22%.[1]
- Meta-analyses of RCTs suggest a possible protective effect of SGLT-2i for DR,[2,3] though
  - DR was not a pre-specified primary endpoint in RCTs and was typically reported as adverse or safety event.

1. Inzucchi et al. Diabetes Care. 2019; 2. Zhou et al. Frontiers in Endocrinology 2022; 3. Tang et al. Diabetes Obes Metab. 2018.

Objective

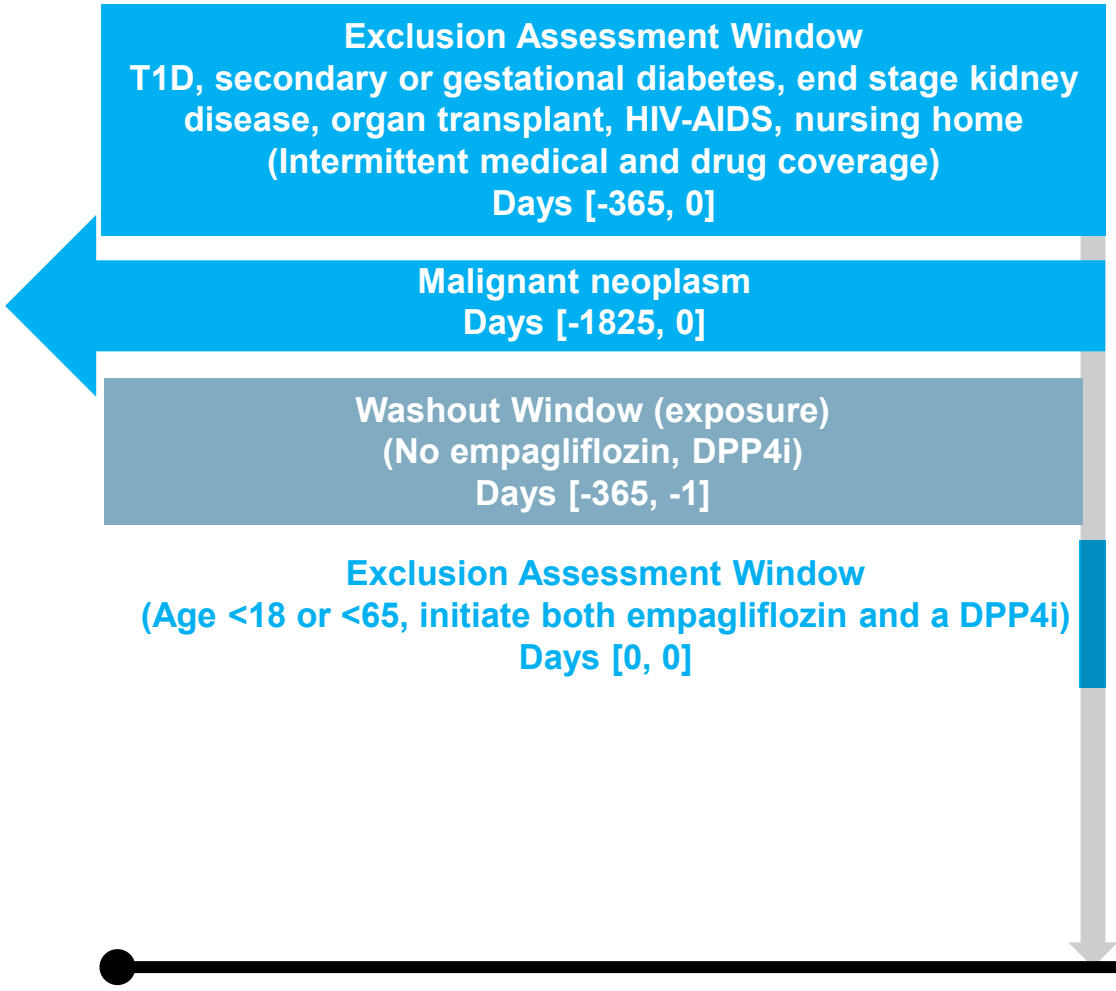
- Objective: We sought to assess the risk of non-proliferative DR (NPDR) onset (cohort 1) and the risk of DR progression (cohort 2) comparing initiation of empagliflozin vs. dipeptidyl peptidase-4 inhibitors (DPP4i) in routine care.

Study design and data source

- **Study design**: New-user active-comparator cohort study with 2 pair-wise comparisons:
  - Empagliflozin vs. DPP4i for onset of NPDR (cohort 1)
  - Empagliflozin vs. DPP4i for DR progression (cohort 2)
- **Data sources**: Optum Clinformatics Data Mart (CDM), IBM® Marketscan®, and Medicare fee-for-service (FFS)
  - U.S. nationwide electronic healthcare database of commercially (18+ years old) and federally insured Americans (65+ years old)
  - Complete enrollment, demographic information, medical inpatient and outpatient claims, and filled prescriptions

New-user active-comparator cohort study (cohort 1)

Exposure-based Cohort Entry Date
(First prescription of empagliflozin or a DPP4i between 08/2014 and 09/2019)
Day 0



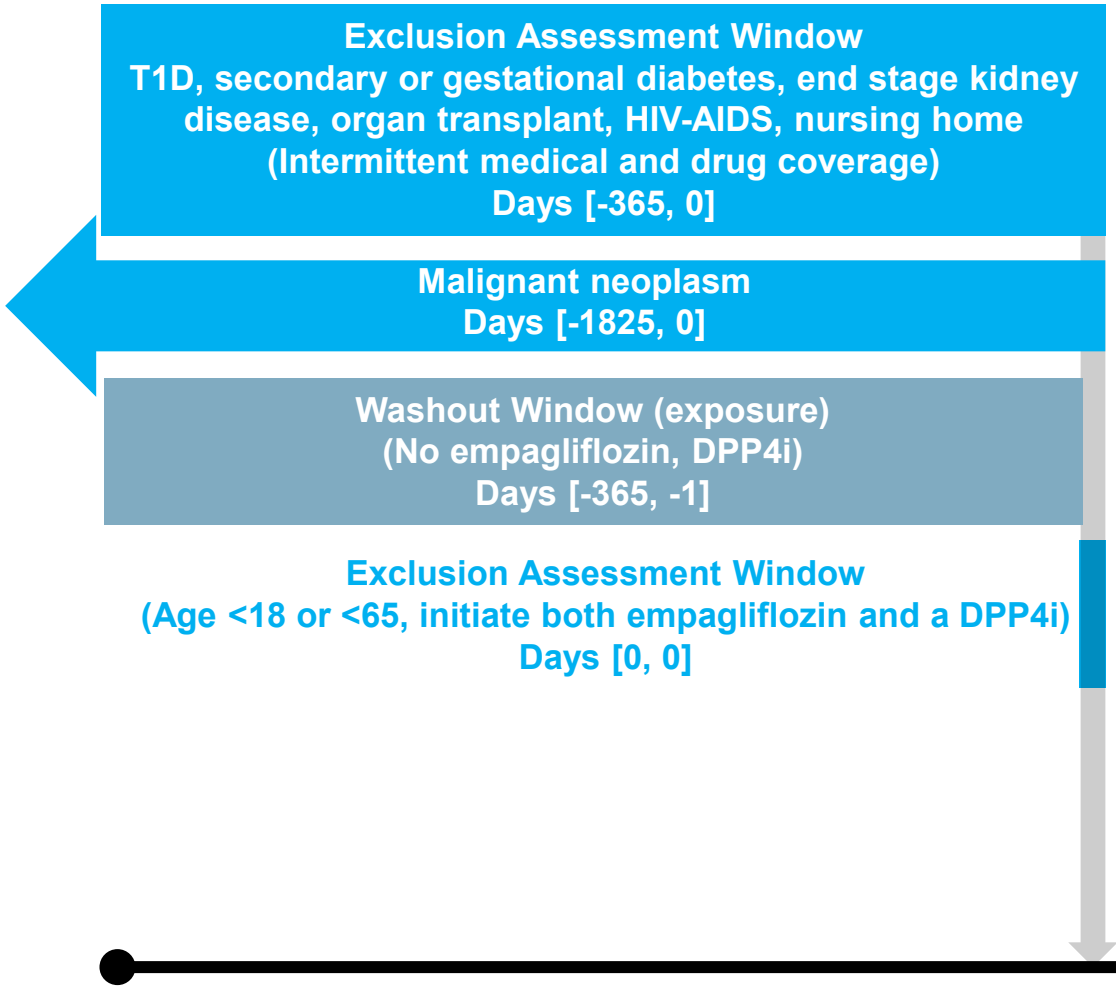
Study population: Patients with T2D initiating empagliflozin or a DPP4i

- Required routine vision or retinal exam or provider (ophthalmologist or optometrist) visit during baseline period
- Excluded
  - patients with history of proliferative DR
  - age-related macular degeneration
  - central/branch retinal vein occlusion
  - vitreous hemorrhage
  - panretinal photocoagulation
  - vitrectomy
  - intravitreal anti-VEGF injection
  - diabetic retinopathy diagnosis

Anti-VEGF: Anti-vascular endothelial growth factor

New-user active-comparator cohort study (cohort 2)

Exposure-based Cohort Entry Date
(First prescription of empagliflozin or a DPP4i between 08/2014 and 09/2019)
Day 0



Study population: Patients with T2D initiating empagliflozin or a DPP4i

- Required history of NPDR diagnosis
- Excluded
  - patients with history of PDR
  - age-related macular degeneration
  - central/branch retinal vein occlusion
  - vitreous hemorrhage
  - panretinal photocoagulation
  - vitrectomy
  - intravitreal anti-VEGF injection
  - diabetic retinopathy diagnosis

Anti-VEGF: Anti-vascular endothelial growth factor

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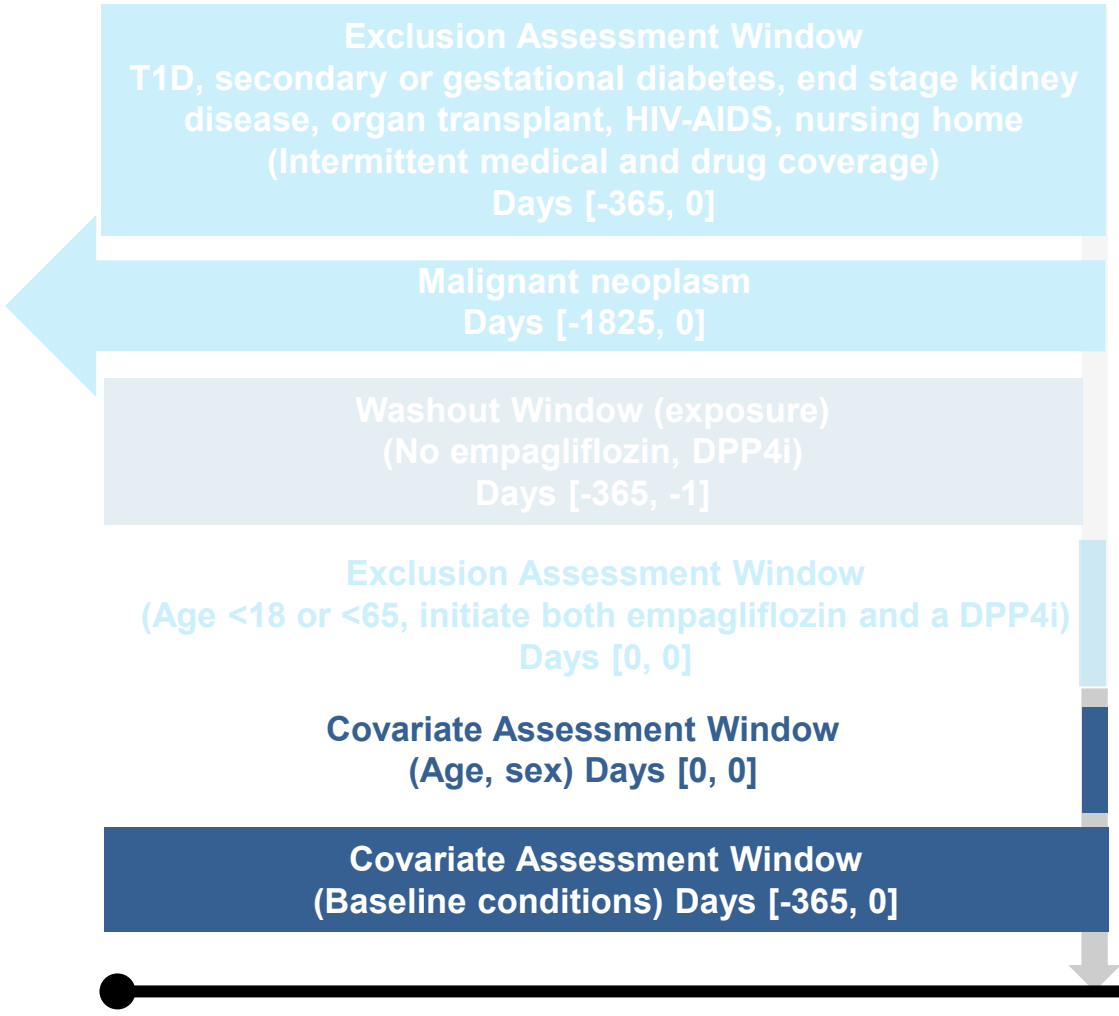

Baseline covariates: 143 confounders measured in the 12 months prior to drug initiation

New-user active-comparator cohort study

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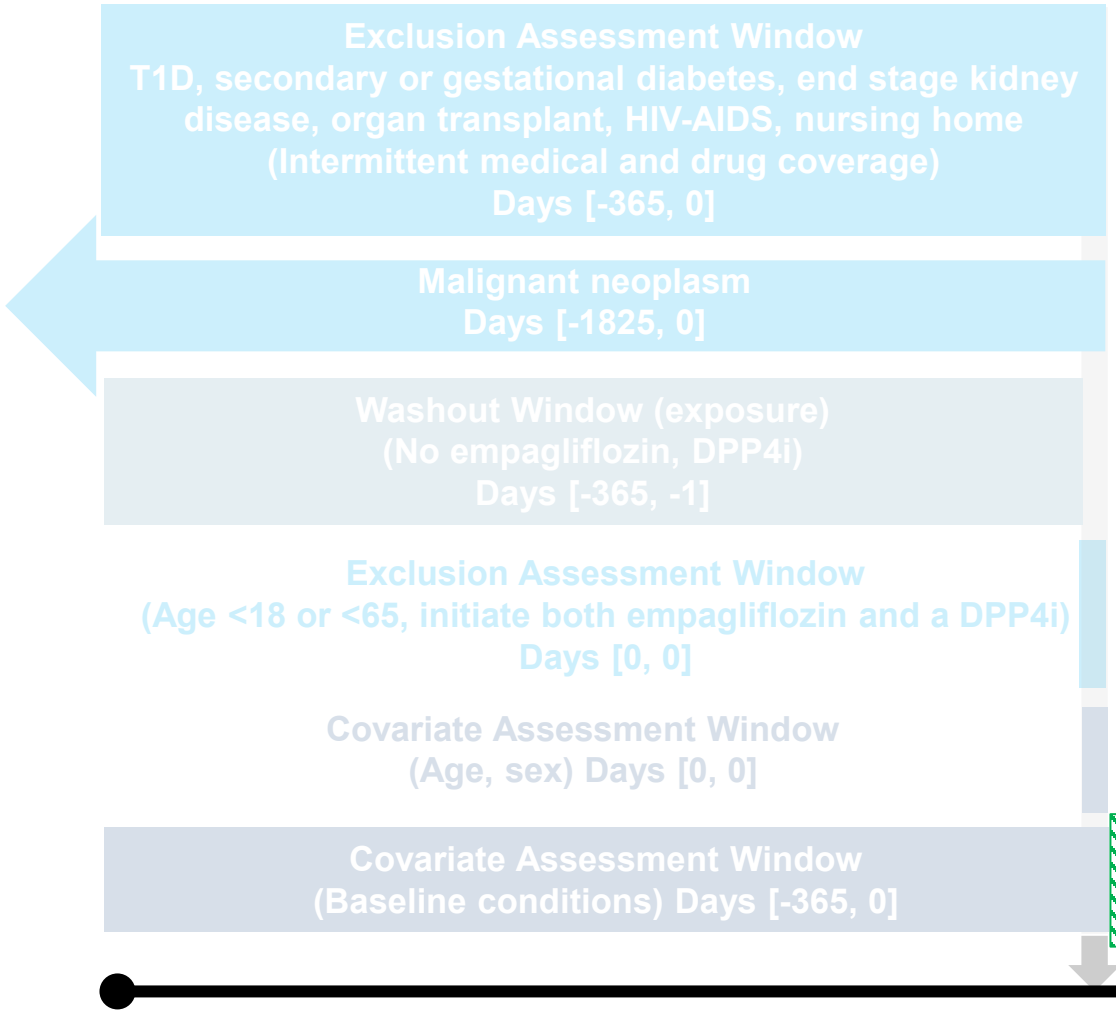


Follow-up started on the day after drug initiation in an as-treated approach

* Earliest of: outcome of interest, switching or discontinuation of study drugs, death, disenrollment, end of the study period

Cohort 1 Outcome

OUTCOME:

Onset of NPDR (ICD codes for mild, moderate, and severe NPDR in any position, any setting)

Cohort 2 Outcome

OUTCOME:

DR progression measured using diagnosis or procedure codes as a composite of

- Intravitreal anti-VEGF injection initiation or
- Panretinal photocoagulation initiation or
- Onset of vitreous hemorrhage or
- Onset of PDR

PDR: Proliferative diabetic retinopathy
Anti-VEGF: Anti-vascular endothelial growth factor

Statistical analysis

- 1:1 Propensity score (PS) matching (nearest neighbor caliper=0.01 of PS)
  - PS estimated on the basis of 143 baseline covariates:

Demographics	Age, sex, race, calendar time (in years)
Indicators of diabetes severity	N antidiabetic medications, insulin use, diabetic nephropathy, neuropathy, diabetes with other ophthalmic manifestations, diabetic foot, N HbA1c test ordered, etc.
Other comorbidities	Hypertension, dyslipidemia, cardiovascular disease, peripheral arterial disease or surgery, chronic kidney disease, etc.
Use of medications	Past or concomitant use of antidiabetic medications, anticoagulants, anti-hypertensives, lipid-lowering medications, etc.
Healthcare utilization measures	Hospitalizations, electrocardiogram, cardiologist visit, etc.

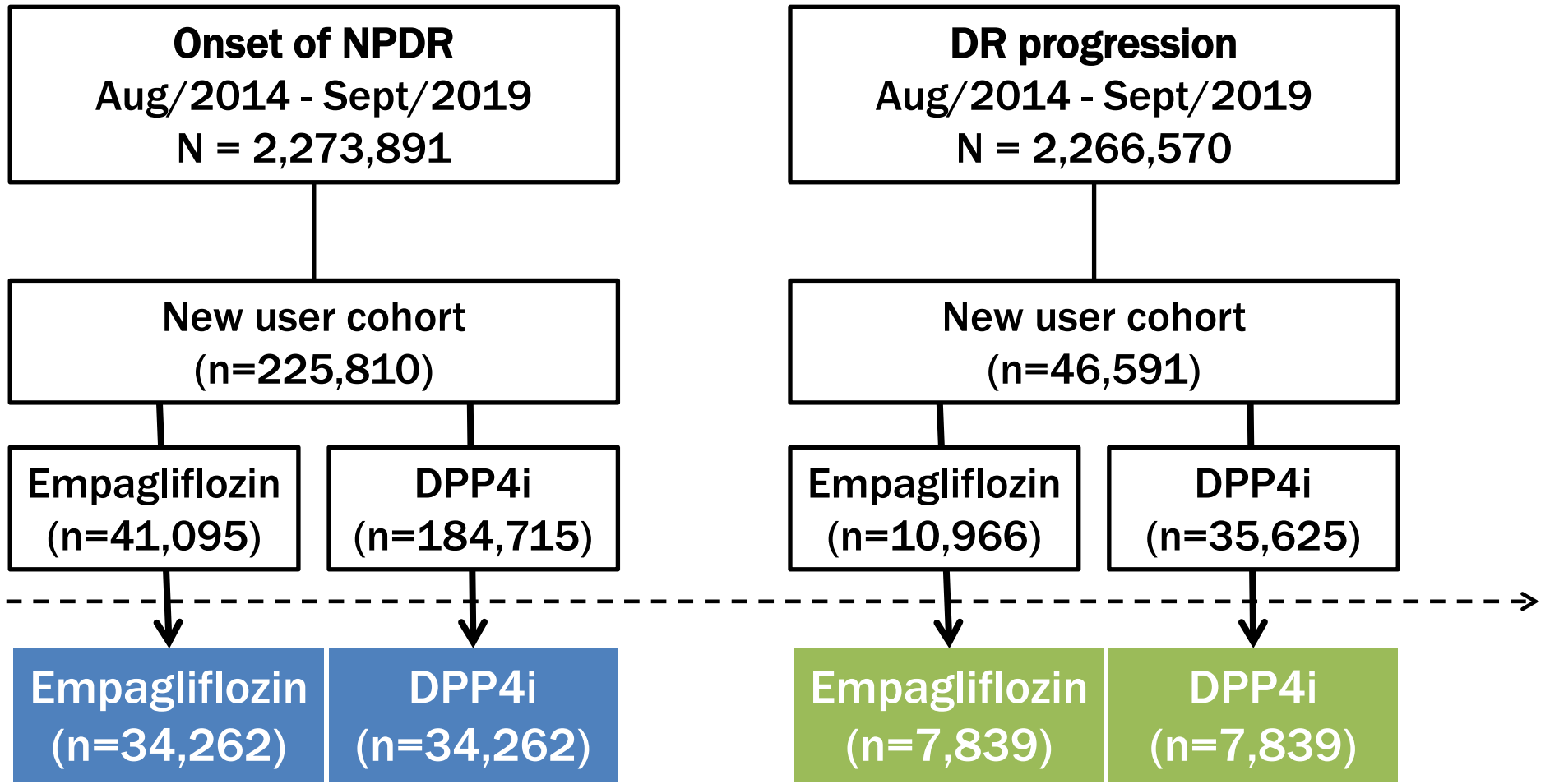
Statistical analysis *cont.*

- 1:1 Propensity score (PS) matching (nearest neighbor caliper=0.01 of PS)
  - PS estimated on the basis of 143 baseline covariates
- Hazard ratios (HR) and incidence rate differences (RD) with their 95% confidence intervals (CI)
- Cumulative incidence plots
- Pooling of results using fixed-effects meta-analysis

Study cohorts

Empagliflozin or a DPP4i with 1-year continuous enrollment

Excluded:
Prevalent SGLT2i or DPP4i users
<18 or <65 years
Patients without T2D
Other exclusion criteria



Selected patient characteristics – After 1:1 PS-matching

	Onset of NPDR (cohort 1)			DR progression (cohort 2)		
Characteristics	Empagliflozin (N = 34,262)	DPP4i (N = 34,262)	Stand. Diff.	Empagliflozin (N = 7,839)	DPP4i (N = 7,839)	Stand. Diff.
Age, mean (SD)	65.67 (7.81)	65.64 (7.70)	0.00	66.91 (7.46)	66.97 (7.51)	0.01
Male, n (%)	17,906 (52.3%)	17,842 (52.1%)	0.00	4,112 (52.5%)	4,088 (52.1%)	0.01
Diabetes with ophthalmic manifestations other than DR, n (%)	1,127 (3.3%)	1,114 (3.3%)	0.00	501 (6.4%)	508 (6.5%)	0.00
Hypertension, n (%)	28,705 (83.8%)	28,778 (84.0%)	0.01	6,790 (86.6%)	6,792 (86.6%)	0.00
Hyperlipidemia, n (%)	28,234 (82.4%)	28,209 (82.3%)	0.00	6,475 (82.6%)	6,498 (82.9%)	0.01
Cardiovascular disease history, n (%)	12,553 (36.6%)	12,550 (36.6%)	0.00	3,410 (43.5%)	3,411 (43.5%)	0.00
Ischemic stroke, n (%)	2,927 (8.5%)	2,905 (8.5%)	0.00	815 (10.4%)	798 (10.2%)	0.01
Heart failure, n (%)	2.895 (8.4%)	2,943 (8.6%)	0.01	949 (12.1%)	966 (12.3%)	0.01
Chronic kidney disease, n (%)	3,688 (10.8%)	3,802 (11,1%)	0.01	1,258 (16.0%)	1,258 (16.0)	0.00
N diabetes drugs, mean (SD)	1.26 (0.86)	1.25 (0.84)	0.01	1.46 (0.88)	1.46 (0.88)	0.00
Current use of metformin; n (%)	22,698 (66.2%)	22,752 (66.4%)	0.00	5.101 (65.1%)	5,064 (64.6%)	0.01
Current use of insulin; n (%)	4,075 (11.9%)	4,039 (11.8%)	0.00	1,939 (24.7%)	1,946 (24.8%)	0.00
HbA1C, %, mean (SD)*	8.70 (2.26)	8.65 (2.24)	0.02	9.31 (2.29)	9.14 (2.34)	0.07

*available for a subset of patients, thus not included in the PS model

Results (cohort 1)

Onset of NPDR	Empagliflozin	DPP4i
N events (IR/1000 PY)	738 (31.07)	705 (29.55)
HR (95% CI)	1.05 (0.95, 1.16)	
RD/1000 PY (95% CI)	1.52 (-1.61, 4.65)	

Mean follow-up time: 8.5 months
IR: incidence rates; PY: person-years; CI: confidence interval
HR: hazard ratio; RD: rate difference

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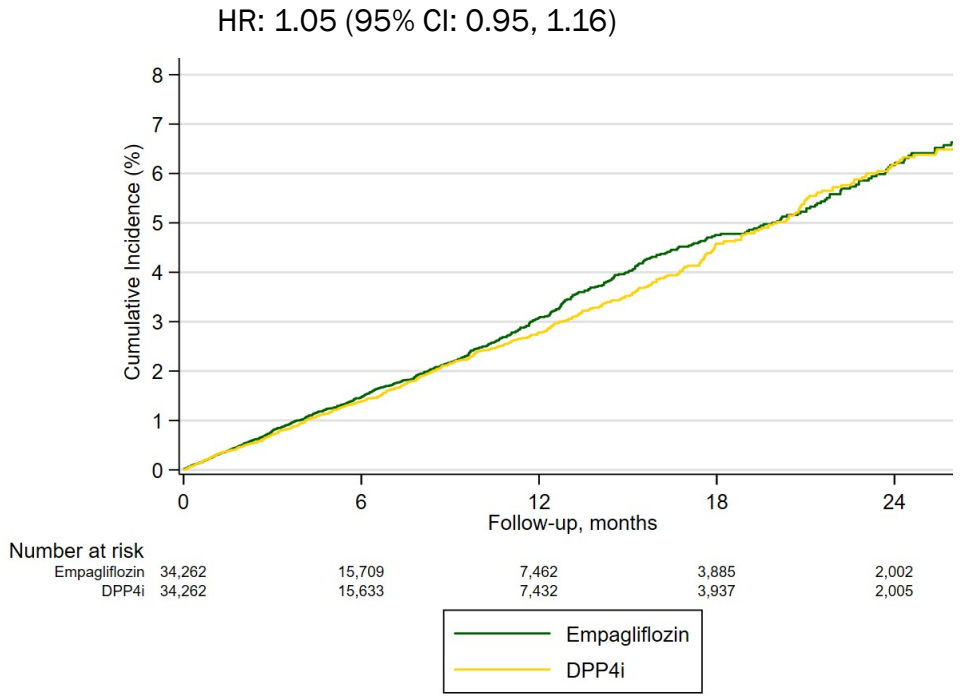

Mean follow-up time: 8.5 months
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Results (cohort 2)

DR progression	Empagliflozin	DPP4i
N events (IR/1000 PY)	154 (30.57)	195 (40.07)
HR (95% CI)	0.77 (0.62, 0.95)	
RD/1000 PY (95% CI)	-9.49 (-16.90, -2.08)	

Mean follow-up time: 8 months
IR: incidence rates; PY: person-years; CI: confidence interval
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Results (cohort 2)

DR progression	Empagliflozin	DPP4i
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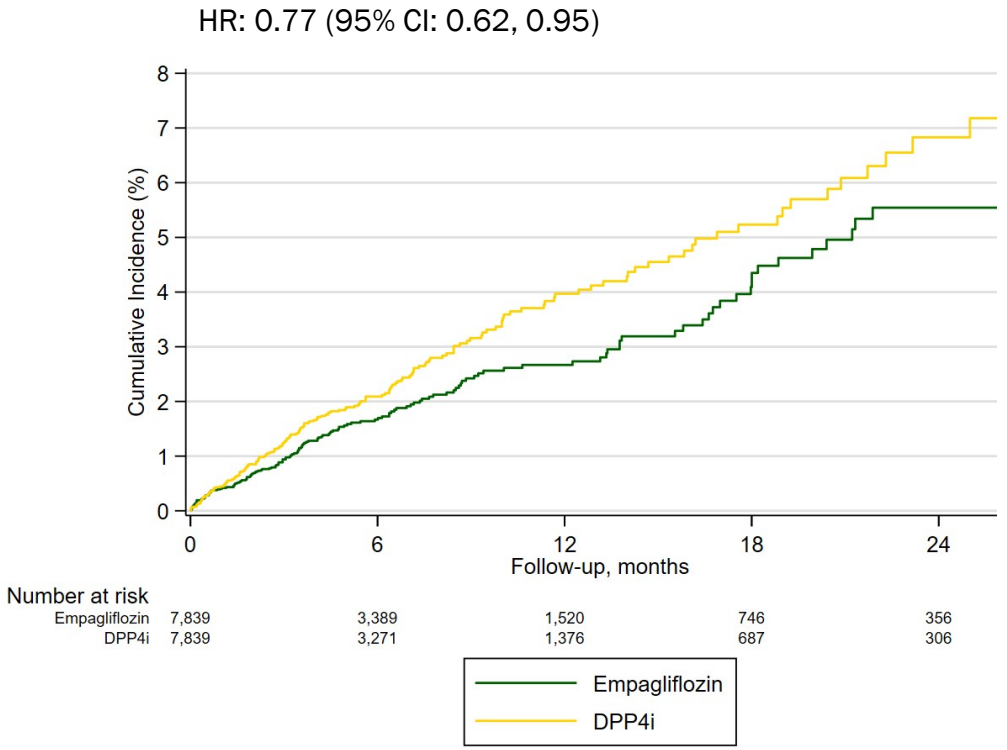

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Conclusions

- In this population-based PS-matched cohort study of adults with T2D (mean follow-up ~8 months), the initiation of empagliflozin, compared with DPP-4i was associated with similar risk of NPDR onset and a 23% reduction in the risk of DR progression.
- Results were consistent in direction and magnitude with a similarly defined DR progression outcome in a post-hoc analysis of the EMPA-REG OUTCOME trial.
- Our data suggest that the initiation of empagliflozin may be beneficial in patients with DR.
- These results may be helpful when weighing the potential risks and benefits of various glucose-lowering agents in adults with T2D and DR.

Thank-You: htesfaye@partners.org

Investigators:

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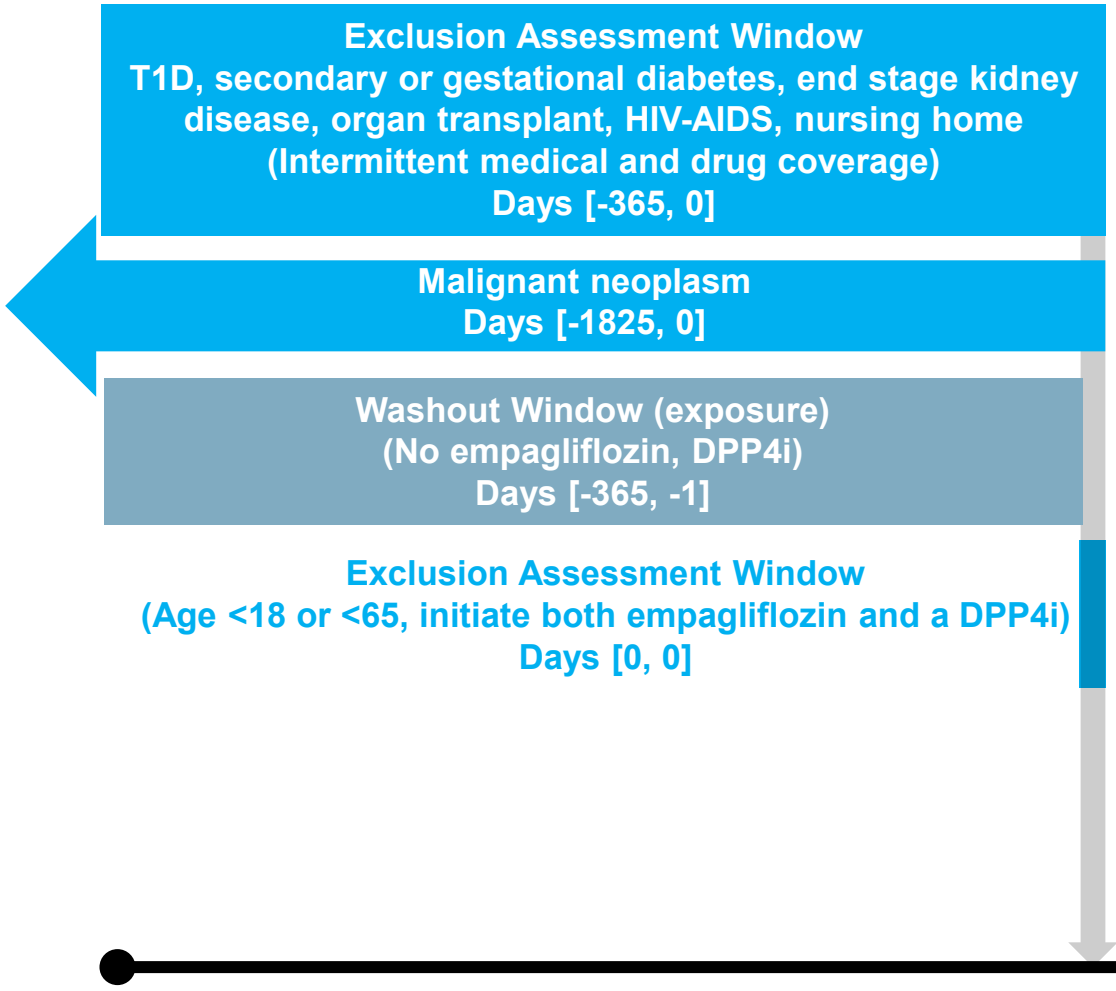

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  - intravitreal anti-VEGF injection,
  - diabetic retinopathy diagnosis

PDR: Proliferative diabetic retinopathy
Anti-VEGF: Anti-vascular endothelial growth factor

Results

Outcome	Empagliflozin N events (IR/1000 PY)	DPP4i N events (IR/1000 PY)	HR 95% CI	RD/1000 PY 95% CI
Onset of NPDR	550 (29.99)	587 (31.57)	0.95 (0.85, 1.07)	-1.58 (-5.16, 2.00)

Mean follow-up time: 8.5 months
IR: incidence rates; PY: person-years; CI: confidence interval
HR: hazard ratio; RD: rate difference