DiabeteScan

Episode 2

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Comparative Effectiveness and Safety of Sodium–Glucose Cotransporter 2 Inhibitors Versus Glucagon-Like Peptide 1 Receptor Agonists in Older Adults

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Diabetes Care 2021;44:826–835 | https://doi.org/10.2337/dc20-1464

Patorno et al, Diabetes Care 2021;44:826–835

Research in context

What is currently known?

- Both sodium–glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor agonists demonstrated cardiovascular benefits in randomized controlled trials of patients with type 2 diabetes generally <65 years old and mostly with cardiovascular disease
- The effectiveness and safety of SGLT2i and GLP-1RA among real-world older adults has not been fully established

What is the key question?

What is the difference in the effectiveness and safety of SGLT2i and GLP-1RA in older adults?

Patorno et al, Diabetes Care 2021;44:826–835

Aims and methods

Aims/hypothesis:

- to evaluate the comparative effectiveness and safety of SGLT2i and GLP-1RA among real-world older adults

Methods:

- Using Medicare data (April 2013–December 2016) authors identified 90,094 propensity score–matched (1:1) T2D patients ‡66 years old initiating SGLT2i or GLP-1RA

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Primary outcomes:

- major adverse cardiovascular events (MACE) (i.e., myocardial infarction, stroke, or cardiovascular death) and hospitalization for heart failure (HHF).

Other outcomes:

- diabetic ketoacidosis (DKA), genital infections, fractures, lower-limb amputations (LLA), acute kidney injury (AKI), severe urinary tract infections and overall mortality.

Hazard ratios (HRs) and rate differences (RDs) per 1,000 person-years, controlling for 140 baseline covariates were estimated

Key message

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Selected baseline characteristics:

Table 1—Selected baseline characteristics of patients initiating SGLT2i versus GLP-1RA before and after 1:1 PS matching

	Before PS matching			After PS matching		
Baseline characteristics	SGLT2i (*N* = 72,900)	GLP-1RA (*N* = 64,417)	St. Diff.	SGLT2i (*N* = 45,047)*	GLP-1RA (*N* = 45,047)*	St. Diff.
Demographics						
Age, mean (SD)	71.98 (5.28)	71.43 (4.94)	0.11	71.56 (5.01)	71.56 (5.03)	0.00
Male, *n* (%)	35,982 (49.4)	28,044 (43.5)	0.12	20,541 (45.6)	20,720 (46.0)	−0.01
Race/ethnicity, *n* (%)						
White	58,251 (79.9)	54,125 (84.0)	−0.11	37,588 (83.4)	37,520 (83.3)	0.00
Black	5,281 (7.2)	4,997 (7.8)	−0.02	3,396 (7.5)	3,388 (7.5)	0.00
Asian	3,434 (4.7)	1,433 (2.2)	0.14	1,138 (2.5)	1,177 (2.6)	−0.01
Hispanic	2,601 (3.6)	1,719 (2.7)	0.05	1,284 (2.9)	1,300 (2.9)	0.00
Other	3,333 (4.6)	2,143 (3.3)	0.06	1,641 (3.6)	1,662 (3.7)	−0.01
Burden of comorbidities, mean (SD)						
Combined Comorbidity Score†	2.94 (2.03)	3.45 (2.32)	−0.23	3.16 (2.15)	3.17 (2.15)	0.00
Frailty score (29)	0.18 (0.06)	0.19 (0.06)	−0.17	0.19 (0.06)	0.19 (0.06)	0.00
Diabetes-related conditions, *n* (%)						
Diabetic nephropathy	6,614 (9.1)	9,850 (15.3)	−0.19	5,132 (11.4)	5,122 (11.4)	0.00
Diabetic retinopathy	7,664 (10.5)	7,888 (12.2)	−0.05	4,966 (11.0)	4,958 (11.0)	0.00
Diabetic neuropathy	17,187 (23.6)	18,251 (28.3)	−0.11	11,721 (26.0)	11,709 (26.0)	0.00
Diabetes with peripheral circulatory disorders	5,841 (8.0)	5,689 (8.8)	−0.03	3,708 (8.2)	3,783 (8.4)	−0.01
Diabetic foot	1,897 (2.6)	2,329 (3.6)	−0.06	1,378 (3.1)	1,393 (3.1)	0.00
Lower-extremity amputation	264 (0.4)	355 (0.6)	−0.03	210 (0.5)	204 (0.5)	0.00
Hypoglycemia	3,529 (4.8)	3,725 (5.8)	−0.04	2,303 (5.1)	2,330 (5.2)	0.00
DKA	244 (0.3)	298 (0.5)	−0.03	157 (0.3)	182 (0.4)	−0.02

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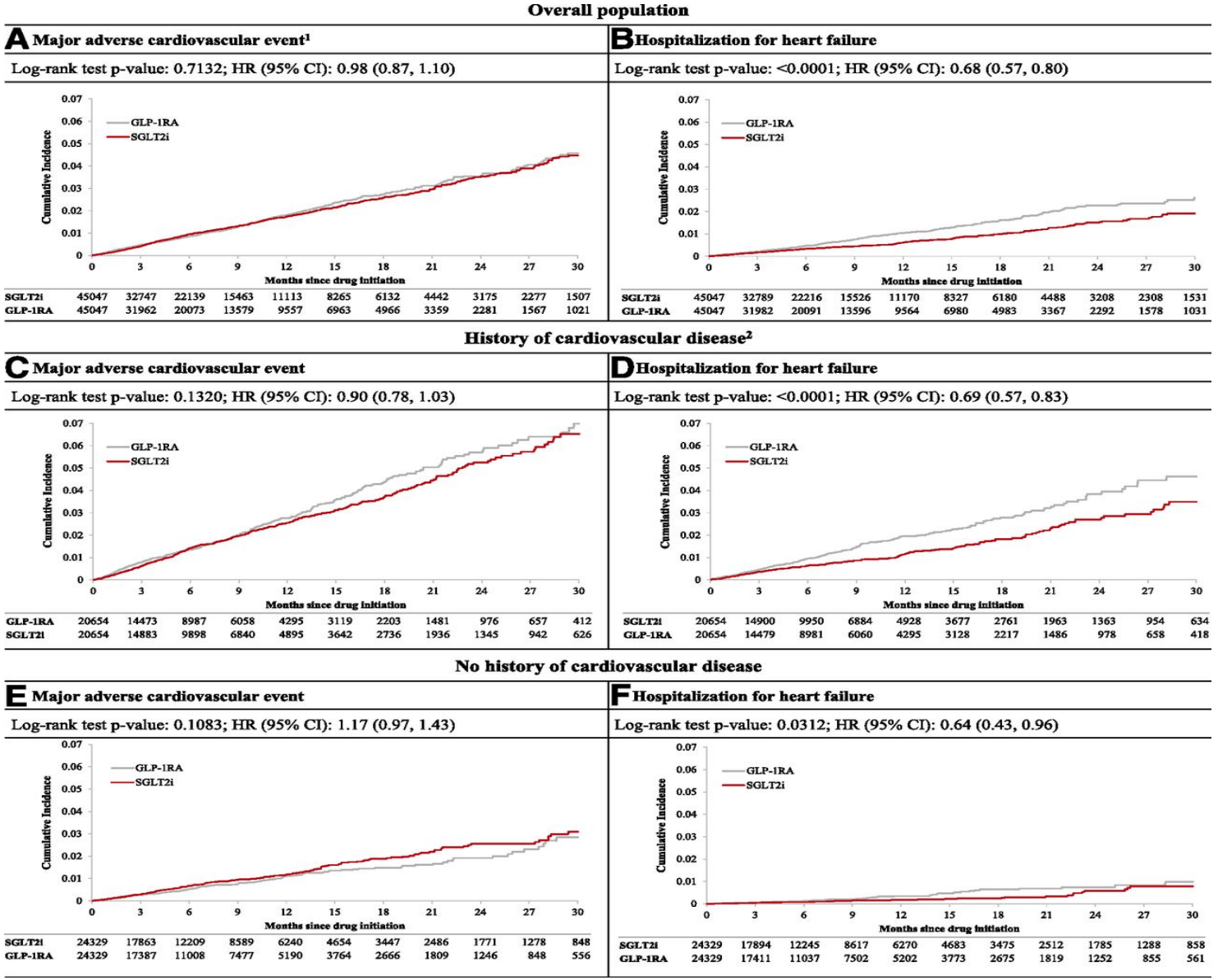
Cumulative incidence for composite cardiovascular outcome and HHF comparing PS-matched SGLT2i vs. GLP-1RA initiators overall and by history of CVD:



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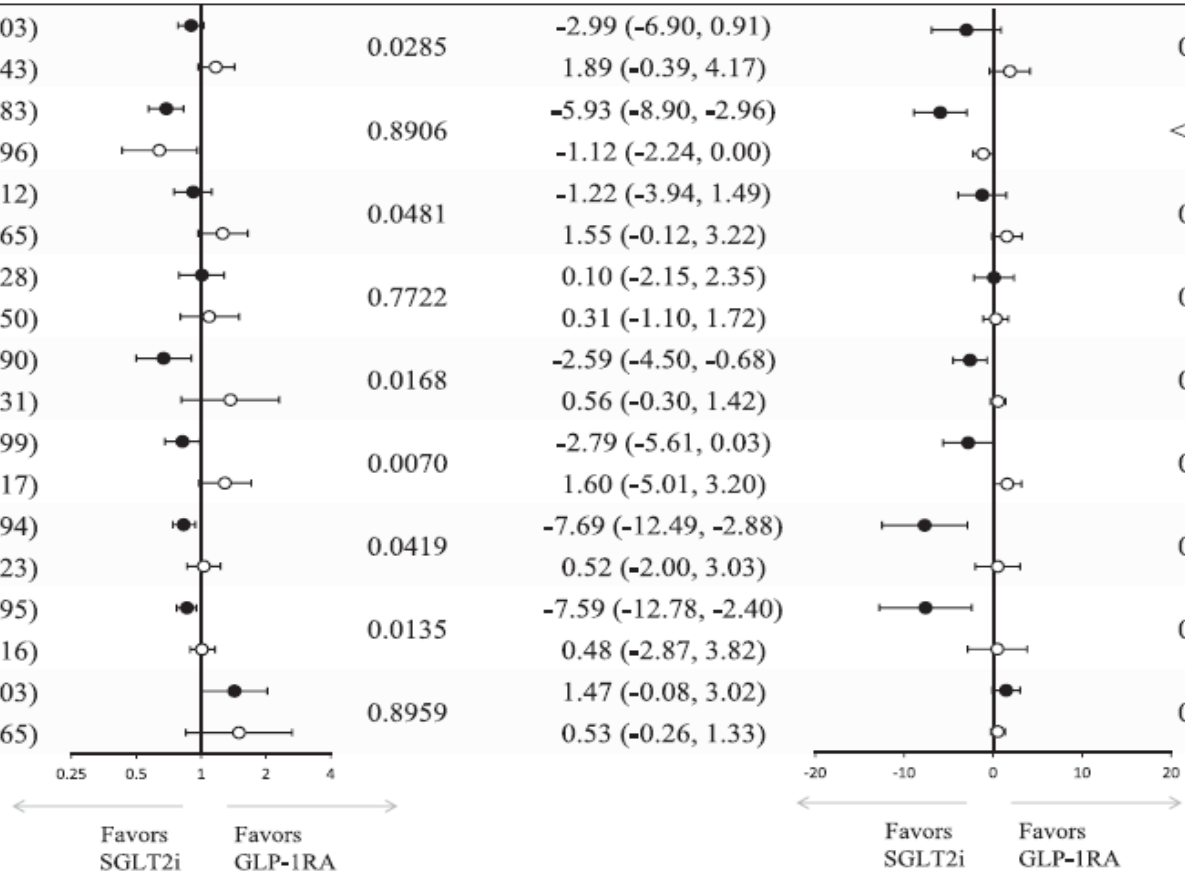
Cardiovascular effectiveness and safety outcomes in subgroups of 1:1 PS-matched initiators of SGLT2i vs. GLP-1RA by history of CVD

Outcome	CVD History	HR (95% CI)	p-value for homogeneity	RD/1000 PY (95% CI)	p-value for homogeneity
Major adverse cardiovascular event (MACE)[2]	History of CVD	0.90 (0.78-1.03)	0.0285	-2.99 (-6.90, 0.91)	0.0201
	No history of CVD	1.17 (0.97-1.43)		1.89 (-0.39, 4.17)	
Hospitalization for heart failure (HHF)	History of CVD	0.69 (0.57-0.83)	0.8906	-5.93 (-8.90, -2.96)	<0.0000
	No history of CVD	0.64 (0.43-0.96)		-1.12 (-2.24, 0.00)	
Myocardial infarction (MI)	History of CVD	0.92 (0.75-1.12)	0.0481	-1.22 (-3.94, 1.49)	0.0661
	No history of CVD	1.26 (0.97-1.65)		1.55 (-0.12, 3.22)	
Ischemic or hemorrhagic stroke	History of CVD	1.01 (0.79-1.28)	0.7722	0.10 (-2.15, 2.35)	0.8684
	No history of CVD	1.09 (0.80-1.50)		0.31 (-1.10, 1.72)	
Cardiovascular mortality	History of CVD	0.67 (0.50-0.90)	0.0168	-2.59 (-4.50, -0.68)	0.0002
	No history of CVD	1.37 (0.81-2.31)		0.56 (-0.30, 1.42)	
All-cause mortality	History of CVD	0.82 (0.68-0.99)	0.0070	-2.79 (-5.61, 0.03)	0.0032
	No history of CVD	1.29 (0.98-1.17)		1.60 (-5.01, 3.20)	
MACE or HHF[3]	History of CVD	0.83 (0.74-0.94)	0.0419	-7.69 (-12.49, -2.88)	0.0006
	No history of CVD	1.03 (0.86-1.23)		0.52 (-2.00, 3.03)	
MI or stroke or HHF or all-cause mortality[4]	History of CVD	0.86 (0.77-0.95)	0.0135	-7.59 (-12.78, -2.40)	0.0007
	No history of CVD	1.01 (0.89-1.16)		0.48 (-2.87, 3.82)	
Lower-limb amputation	History of CVD	1.43 (1.00-2.03)	0.8959	1.47 (-0.08, 3.02)	0.2155
	No history of CVD	1.50 (0.85-2.65)		0.53 (-0.26, 1.33)	



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Number of events, person-time, and incidence rates for safety outcomes:

Table 3—Number of events, person-time, and incidence rates for safety outcomes in 1:1 PS-matched initiators of SGLT2i versus GLP-1RA

			SGLT2i vs. GLP-1RA	
Safety outcomes	SGLT2i (N = 45,047)	GLP-1RA (N = 45,047)	HR (95% CI)	RD/1,000 PY (95% CI)
DKA	79 (2.37)	50 (1.65)	1.46 (1.02, 2.07)	0.72 (0.02, 1.41)
Bone fracture*	181 (5.43)	175 (5.80)	0.94 (0.76, 1.16)	−0.36 (−1.53, 0.81)
LLA	104 (3.12)	67 (2.22)	1.44 (1.06, 1.96)	0.90 (0.10, 1.70)
GIs	2,623 (82.31)	753 (25.23)	3.34 (3.08, 3.62)	57.08 (53.45, 60.70)
AKI	1,268 (38.49)	1,352 (45.54)	0.85 (0.79, 0.92)	−7.05 (−10.27, −3.83)
Severe UTI†	147 (4.41)	161 (5.33)	0.83 (0.67, 1.04)	−0.92 (−2.01, 0.17)

Data are N events (incidence rate/1,000 person-years) unless otherwise indicated. GIs, genital infections; PY, person-years. *Humerus, wrist, hip, and pelvis fracture. †UTI requiring hospitalization.

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Conclusion

- In a large population-based cohort study of 90,000 older adults with T2D, the initiation of SGLT2i versus GLP-1RA was associated with:
- a similar occurrence of MACE,
- 3.2 fewer hospitalizations for heart failure events, 0.7 more diabetic ketoacidosis, 0.9 more lower limb amputations, 57.1 more genital infections, and 7.1 fewer acute kidney injury events over 1,000 person-years.
- SGLT2i appeared to be associated with greater cardiovascular benefit than GLP-1RA among older patients with history of CVD, with less benefit in those without history of CVD.

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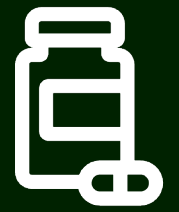
How might this impact clinical practice?

The treatment of GLP-1 RA or SGLT-2i in older adults has generally similar effects as those seen in RCT in younger population.



Among other characteristics, the selection of treatment should be based on the history of heart failure, DKD or CVD.

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Comparative Effectiveness of SGLT2 Inhibitors, GLP-1 Receptor Agonists, DPP-4 Inhibitors, and Sulfonylureas on Risk of Kidney Outcomes: Emulation of a Target Trial Using Health Care Databases

Yan Xie,[1,2,3] Benjamin Bowe,[1,2,3] Andrew K. Gibson,[1,3] Janet B. McGill,[4] Geetha Maddukuri,[5] Yan Yan,[1,6] and Ziyad Al-Aly[1,3,4,5,7]

Diabetes Care 2020;43:2859–2869 | https://doi.org/10.2337/dc20-1890

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Research in context

What is currently known?

- Diabetic kidney disease is very prevalent among T2DM patients and is associated with substantial morbidity and mortality
- Both SGLT2i and GLP-1RA have shown nephroprotectivity in RTC
- Very limited RWE data on the comparison of the effects of sulphonylureas, DPP-4i, GLT2i, GLP-1RA is available

What is the key question?

- *What is the risk of the composite outcome of estimated glomerular filtration rate (eGFR) decline >50%, end-stage kidney disease (ESKD), or all-cause mortality in patients treated with sulphonylureas, DPP-4i, SGLT2i, GLP-1RA?*

Xie et al, Diabetes Care 2020;43:2859–2869

Aims and methods

Aims/hypothesis:

- To assess the risk of the composite outcome of estimated glomerular filtration rate (eGFR) decline >50%, end-stage kidney disease (ESKD), or all-cause mortality in patients treated with sulphonylureas, DPP-4i, SGLT2i, GLP-1RA

Methods:

- VA databases which have provided high-dimensional electronic health records since 1 October 1999 were used
- U.S. veterans initiated on SGLT2i, GLP-1, DPP-4 or sulfonylureas were followed for up to 3 years
- Risks were estimated using survival models adjusted for predefined covariates as well as covariates identified by a high-dimensional variable selection algorithm through application of generalized propensity scores.

Xie et al, Diabetes Care 2020;43:2859–2869

Primary outcome:

- time until the occurrence of the composite outcome of eGFR decline >50%, ESKD, or all-cause mortality

Key message

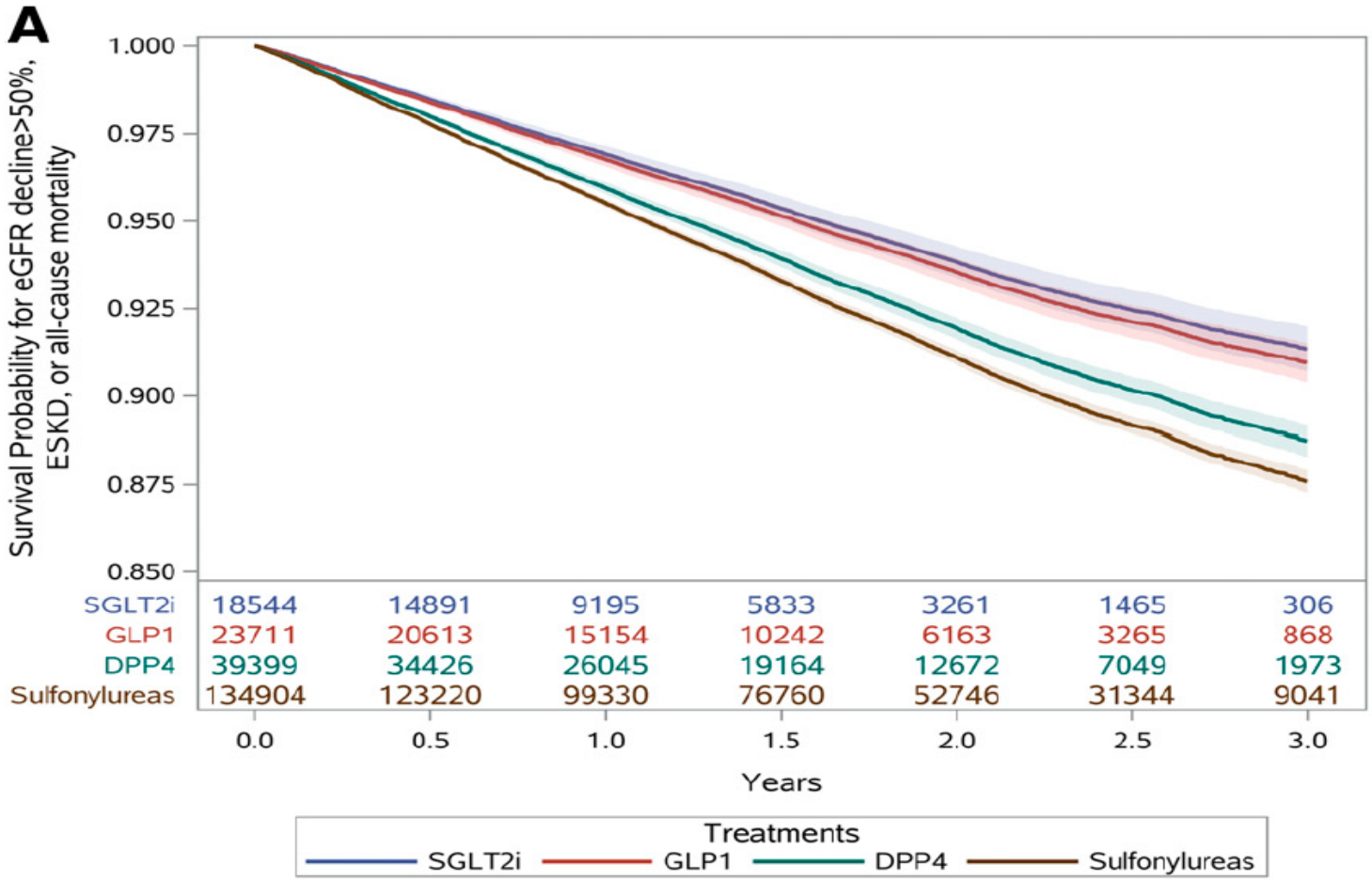
Xie et al, Diabetes Care 2020;43:2859–2869

Selected baseline characteristics:

Cohort characteristic	Overall cohort	SGLT2i	GLP-1	DPP-4	Sulfonylureas
Patients	216,558	18,544 (8.56)	23,711 (10.95)	39,399 (18.19)	134,904 (62.29)
Age (years)	65.46 (11.05)	65.88 (9.10)	64.87 (10.07)	67.06 (11.07)	65.05 (11.41)
Race					
White	155,829 (71.95)	13,624 (73.47)	17,325 (73.07)	28,465 (72.25)	96,405 (71.46)
Black	38,520 (17.79)	2,803 (15.12)	3,712 (15.66)	6,901 (17.52)	25,104 (18.61)
Other	22,219 (10.26)	2,117 (11.42)	2,674 (11.28)	4,033 (10.24)	13,395 (9.93)
Sex					
Male	204,622 (94.49)	17,794 (95.96)	21,818 (92.02)	37,114 (94.20)	127,896 (94.81)
Female	11,936 (5.51)	750 (4.04)	1,893 (7.98)	2,285 (5.80)	7,008 (5.19)
eGFR (mL/min/1.73 m^2)	75.02 (22.53)	76.49 (18.56)	70.67 (23.72)	72.61 (22.62)	76.29 (22.64)
HbA_{1c} (%)	8.57 (2.50)	8.59 (1.51)	8.68 (1.71)	8.35 (4.34)	8.61 (1.92)
HbA_{1c} (mmol/mol)	70 (20.42)	70 (12.31)	71 (13.99)	68 (35.34)	71 (15.83)
BMI (kg/m^2)	33.14 (6.60)	34.27 (6.47)	36.68 (7.06)	32.61 (6.36)	32.52 (6.38)
LDL (mg/dL)	87.90 (39.52)	81.37 (36.27)	80.95 (36.36)	85.91 (37.35)	90.60 (40.79)
Systolic blood pressure (mmHg)	132.94 (17.17)	132.52 (16.81)	132.55 (17.06)	132.57 (16.79)	133.18 (17.35)
Diastolic blood pressure (mmHg)	76.36 (10.55)	74.54 (10.16)	74.63 (10.22)	75.37 (10.41)	77.20 (10.60)
Congestive heart failure	16,258 (7.51)	2,321 (12.52)	2,975 (12.55)	2,500 (6.35)	8,462 (6.27)
Cardiovascular disease	54,389 (25.12)	7,969 (42.97)	6,915 (29.16)	9,537 (24.21)	29,968 (22.21)
Albuminuria*	57,883 (26.73)	5,762 (31.07)	8,171 (34.46)	10,903 (27.67)	33,047 (24.50)
Metformin use†	103,355 (47.73)	10,348 (55.80)	11,751 (49.56)	18,948 (48.09)	62,308 (46.19)
Insulin use†	56,346 (26.02)	11,224 (60.53)	17,908 (75.53)	12,909 (32.76)	14,305 (10.60)
ACE/ARB use†	91,406 (42.21)	10,084 (54.38)	13,360 (56.35)	17,081 (43.35)	50,881 (37.72)
Calcium channel blocker use†	44,264 (20.44)	4,440 (23.94)	6,211 (26.19)	8,380 (21.27)	25,233 (18.70)
β-Blocker use†	65,903 (30.43)	8,300 (44.76)	10,181 (42.94)	11,755 (29.84)	35,667 (26.44)
Diuretic use†	62,304 (28.77)	6,718 (36.23)	9,957 (41.99)	11,103 (28.18)	34,526 (25.59)
Statin use†	114,032 (52.66)	12,321 (66.44)	16,028 (67.60)	21,720 (55.13)	63,963 (47.41)

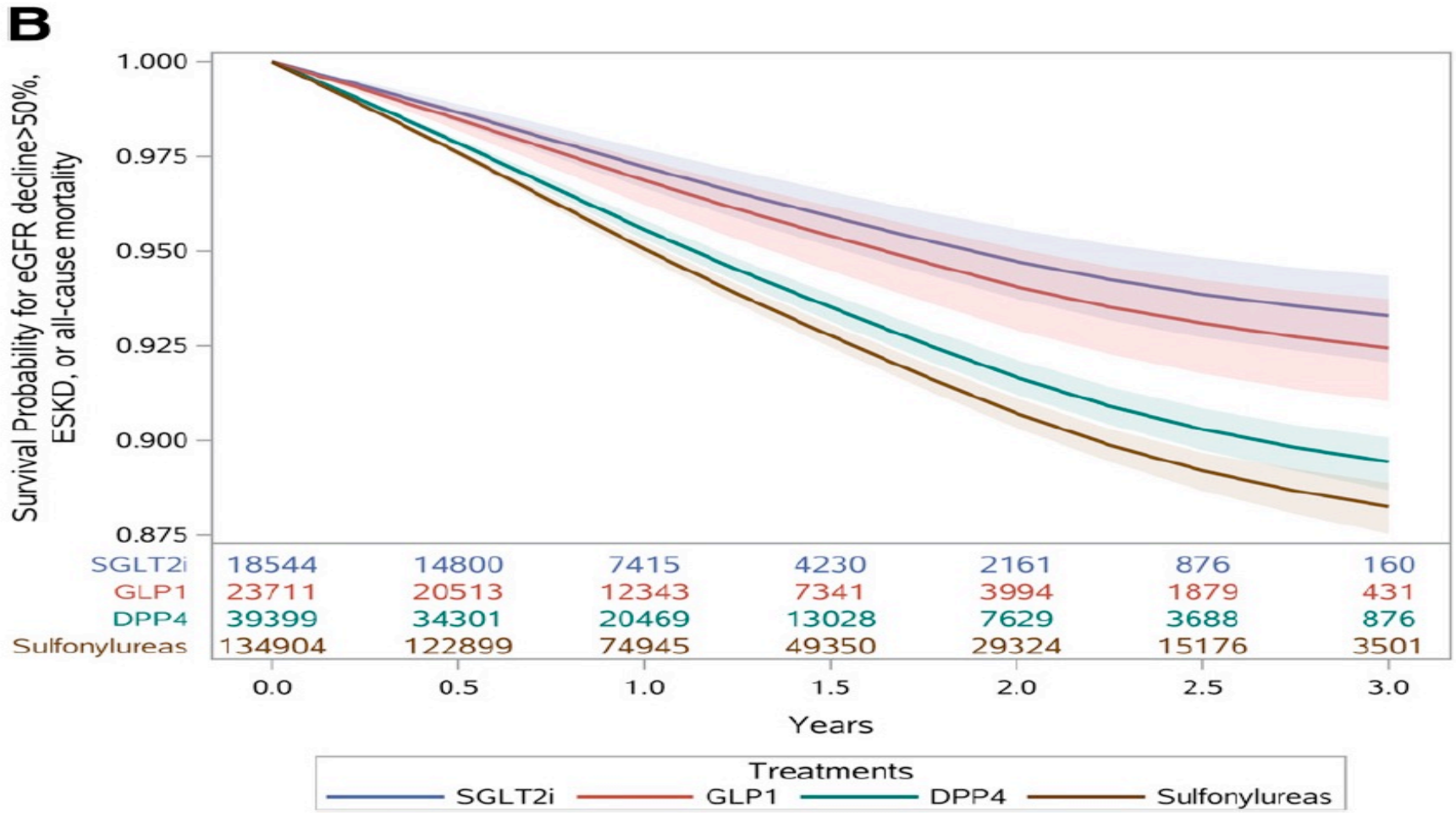
Xie et al, Diabetes Care 2020;43:2859–2869

Adjusted intention-to-treat survival probability for the composite outcome of eGFR decline > 50%, ESKD, or all-cause mortality



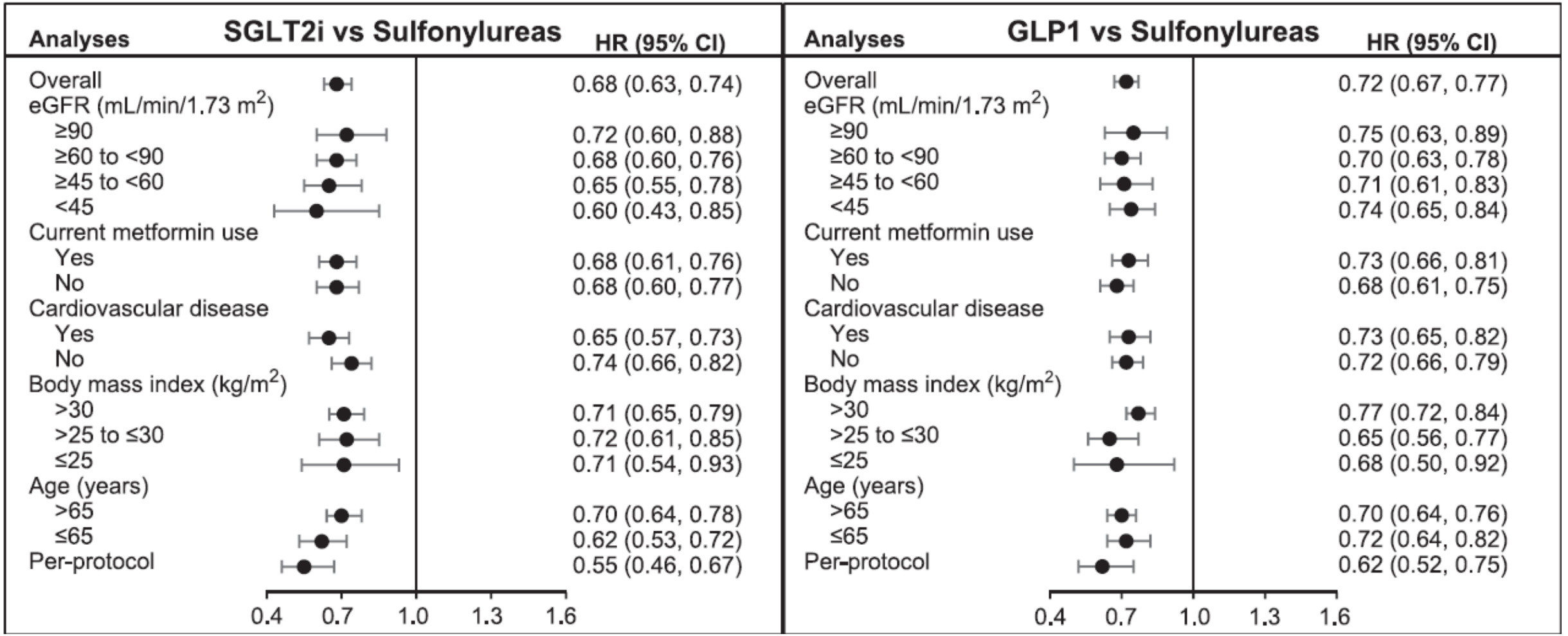
Xie et al, Diabetes Care 2020;43:2859–2869

Adjusted per-protocol survival probability for the composite outcome of eGFR decline >50%, ESKD, or all-cause mortality



Xie et al, Diabetes Care 2020;43:2859–2869

HRs for the composite outcome of eGFR decline > 50%, ESKD, or all-cause mortality



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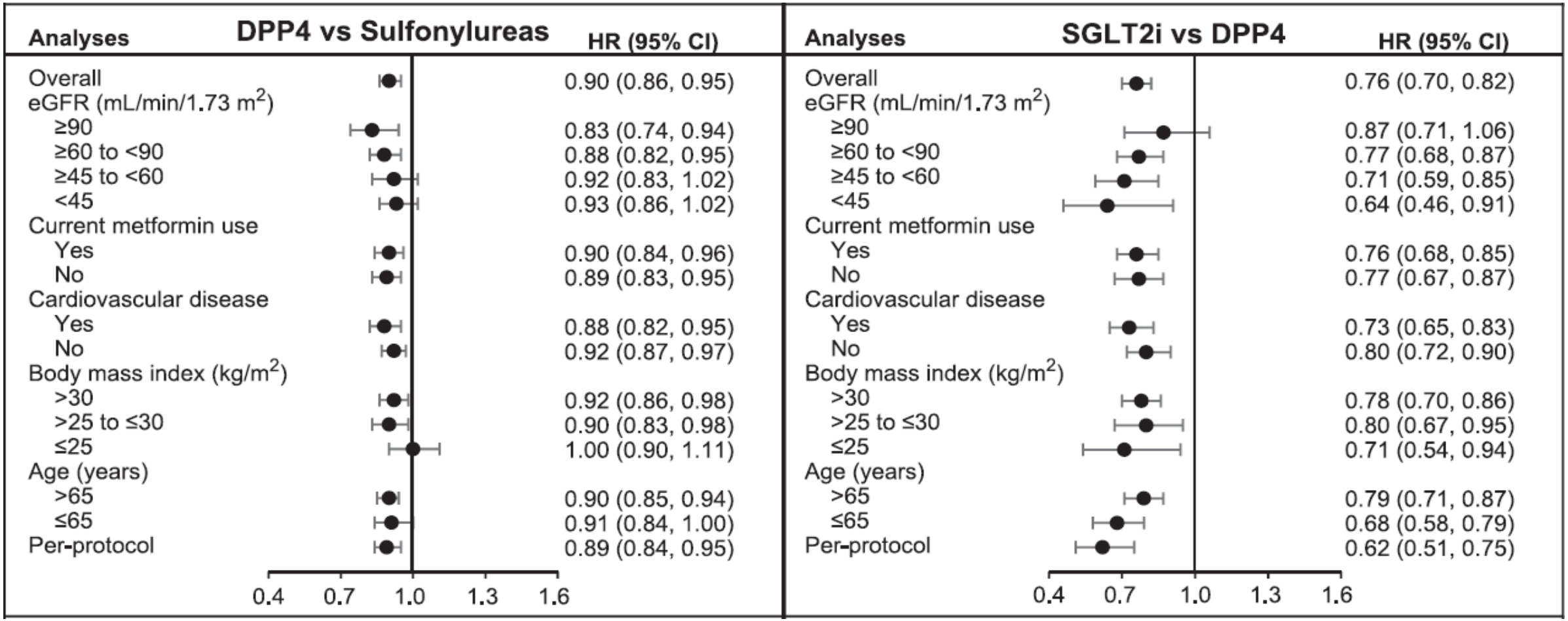

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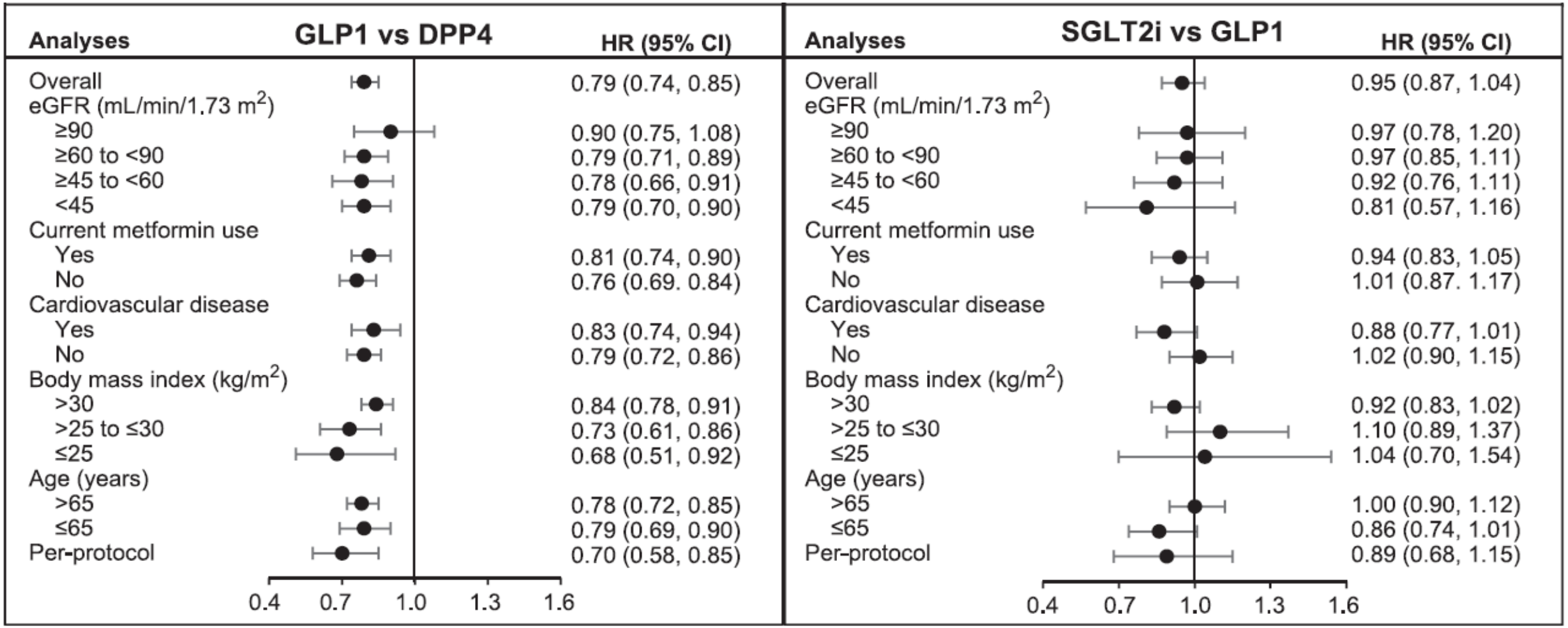


Xie et al, Diabetes Care 2020;43:2859–2869

Conclusions

- This study of 216,558 people with type 2 diabetes provides real-world evidence that compared with those with new use of sulfonylureas, new use of SGLT2i, GLP-1, and DPP-4 was associated with a lower risk of the composite outcome of eGFR decline >50%, ESKD, or all cause mortality.
- No statistically significant difference in risk of the composite outcome between the SGLT2i and GLP-1 groups was found
- Both SGLT2i and GLP-1 had a lower risk of the composite outcome than DPP-4.
- The findings were consistent in multiple sensitivity analyses

Xie et al, Diabetes Care 2020;43:2859–2869

How might this impact clinical practice?

The treatment with DPP-4 inhibitors and, in particular, GLP-1 RA or SGLT-2i provides renal outcomes benefits as compared to sulphonylureas

These RWE data suggest similar renal benefits for GLP-1 RA and SGLT-2i.

Xie et al, Diabetes Care 2020;43:2859–2869

Sustained Intensive Treatment and Long-term Effects on HbA_{1c} Reduction (SILVER Study) by CGM in People With Type 1 Diabetes Treated With MDI

Marcus Lind,[1,2] Arndís F. Ólafsdóttir,[1,2] Irl B. Hirsch,[3] Jan Bolinder,[4] Sofia Dahlqvist,[1] Aldina Pivodic,[5,6] Jarl Hellman,[7] Magnus Wijkman,[8] Erik Schwarcz,[9] Henrik Albrektsson,[5] Tim Heise,[10] and William Polonsky[11,12]

Diabetes Care 2021;44:141–149 | https://doi.org/10.2337/dc20-1468

Lind et al, Diabetes Care 2021;44:141–149

Research in context

What is currently known?

- Continuous glucose monitoring reduces HbA1c and time spent in hypoglycemia in people with type 1 diabetes treated with multiple daily insulin injections when evaluated over shorter time periods.
- It is unclear to what extent CGM improves and helps to maintain glucose control, treatment satisfaction, diabetes distress, hypoglycemic concerns, and overall well-being over longer periods of time.

What is the key question?

- *Does CGM improve and help to maintain glucose control treatment satisfaction, diabetes distress, hypoglycemic concerns, and overall well-being over longer periods of time?*

Lind et al, Diabetes Care 2021;44:141–149

Aims and methods

Aims/hypothesis:

- To explore whether CGM improves and helps to maintain glucose control treatment satisfaction, diabetes distress, hypoglycemic concerns, and overall well-being over longer periods of time

Methods:

- The SILVER study was a 1-year extension of the GOLD trial
- GOLD was a randomized, multicenter crossover trial evaluating the effects of CGM versus SMBG in people with T1D treated with MDI
- All participants received CGM (Dexcom G4 or G5). Clinical visits to a diabetes nurse occurred at weeks 13, 26, 39, and 52.

Lind et al, Diabetes Care 2021;44:141–149

Primary outcome:

- change between HbA1c at the end of the SMBG period in the GOLD study (before long-term CGM use) and at the end of the SILVER study

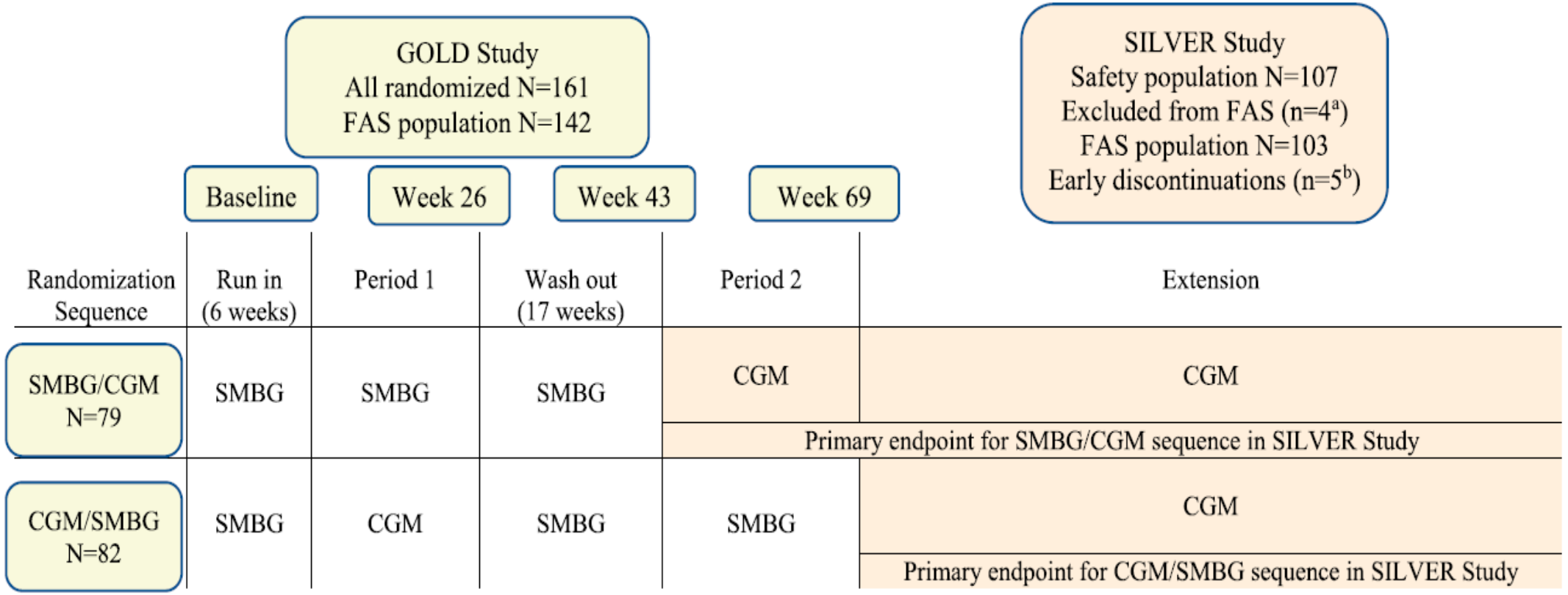
Secondary outcomes:

- Secondary end points were evaluated over the same time period as for HbA1c and were hierarchically tested in the following order:
- 1) time in hypoglycemia (< 3.0 mmol/L [54 mg/dL]);
- 2) time in hypoglycemia (< 4.0 mmol/L [72 mg/dL]);
- 3) time in range (TIR) (4–10 mmol/L [72–180 mg/dL]).

Key message

Lind et al, Diabetes Care 2021;44:141–149

A schematic picture of the study design for GOLD/SILVER showing when the primary and secondary end points were evaluated



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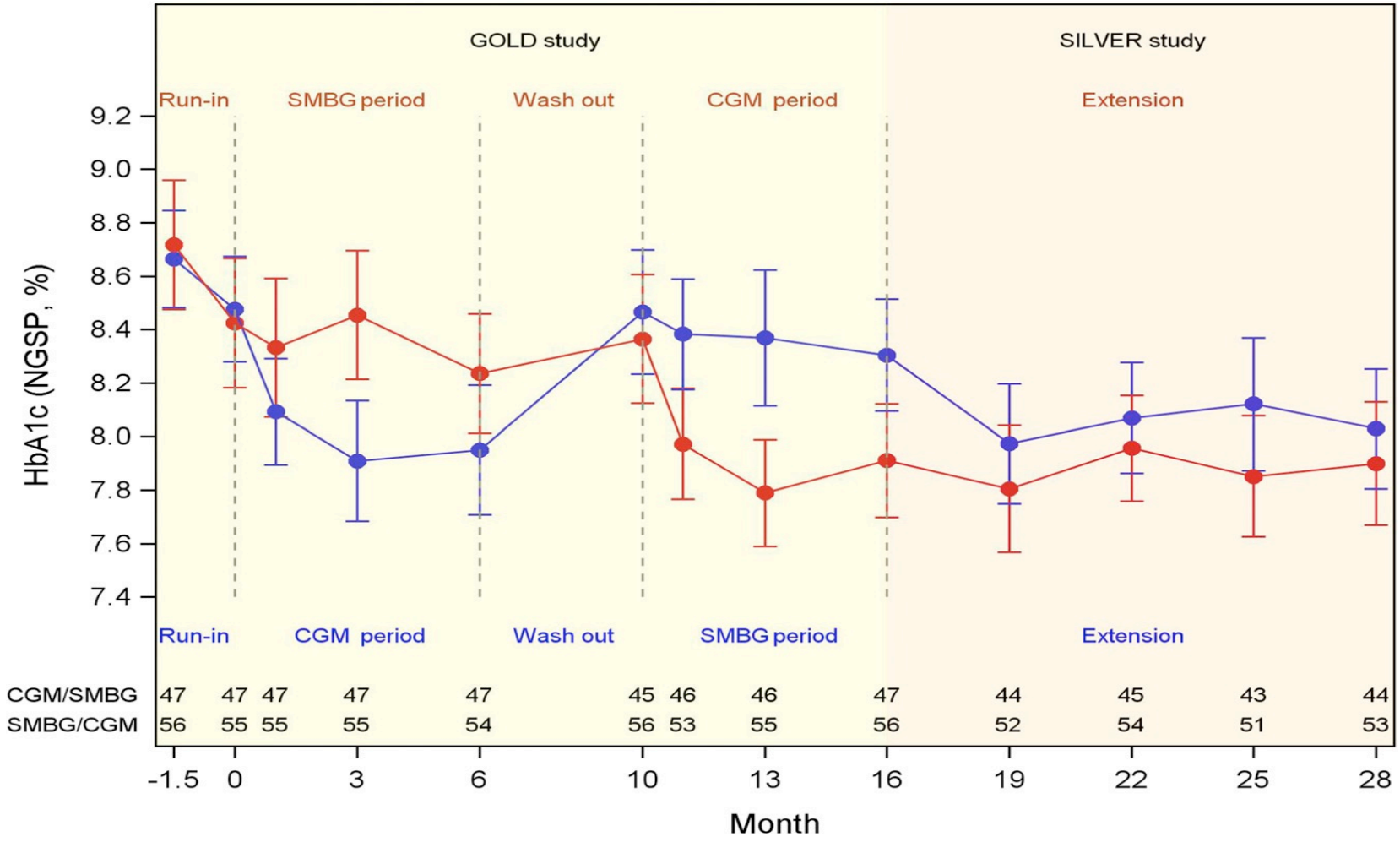
HbA1c levels from the run-in period in the GOLD trial to the end of the SILVER study



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Conclusions

- When comparing with SMBG during the more intensive GOLD trial, HbA1c was 0.35% (3.8 mmol/mol) lower at the end of the current extension study (SILVER) when participants used CGM over 1–1.5 years and with less intensive clinical support.
- Time with very low glucose levels (< 3.0 mmol/L [54 mg/dL]) was reduced by 70%, from 2.1 to 0.6% per 24 h.
- Time in hypoglycemia (< 4.0 mmol/L [72 mg/dL]) per 24 h decreased by 45% during long-termCGM use compared with earlier SMBG
- TIR (4–10 mmol/L [72– 180 mg/dL]) increased by 9%.
- Overall, well-being, treatment satisfaction, and hypoglycemic confidence improved over the same time period; while hypoglycemic fear decreased

Lind et al, Diabetes Care 2021;44:141–149

How might this impact clinical practice?

CGM significantly improves glucose control and well-being of T1DM patients while decreasing the risk of hypoglycemia even when less intensive clinical support was provided

CGM is very beneficial for improving clinical outcomes in the long-term run

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THANK YOU

for your attention

This activity is supported by an unrestricted educational grant provided by Lilly