Lower Atrial Fibrillation Risk with Sodium-Glucose Cotransporter-2 Inhibitors versus Dipeptidyl Peptidase-4 Inhibitors in Individuals with Type 2 Diabetes: A Nationwide Cohort Study

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Disclosure

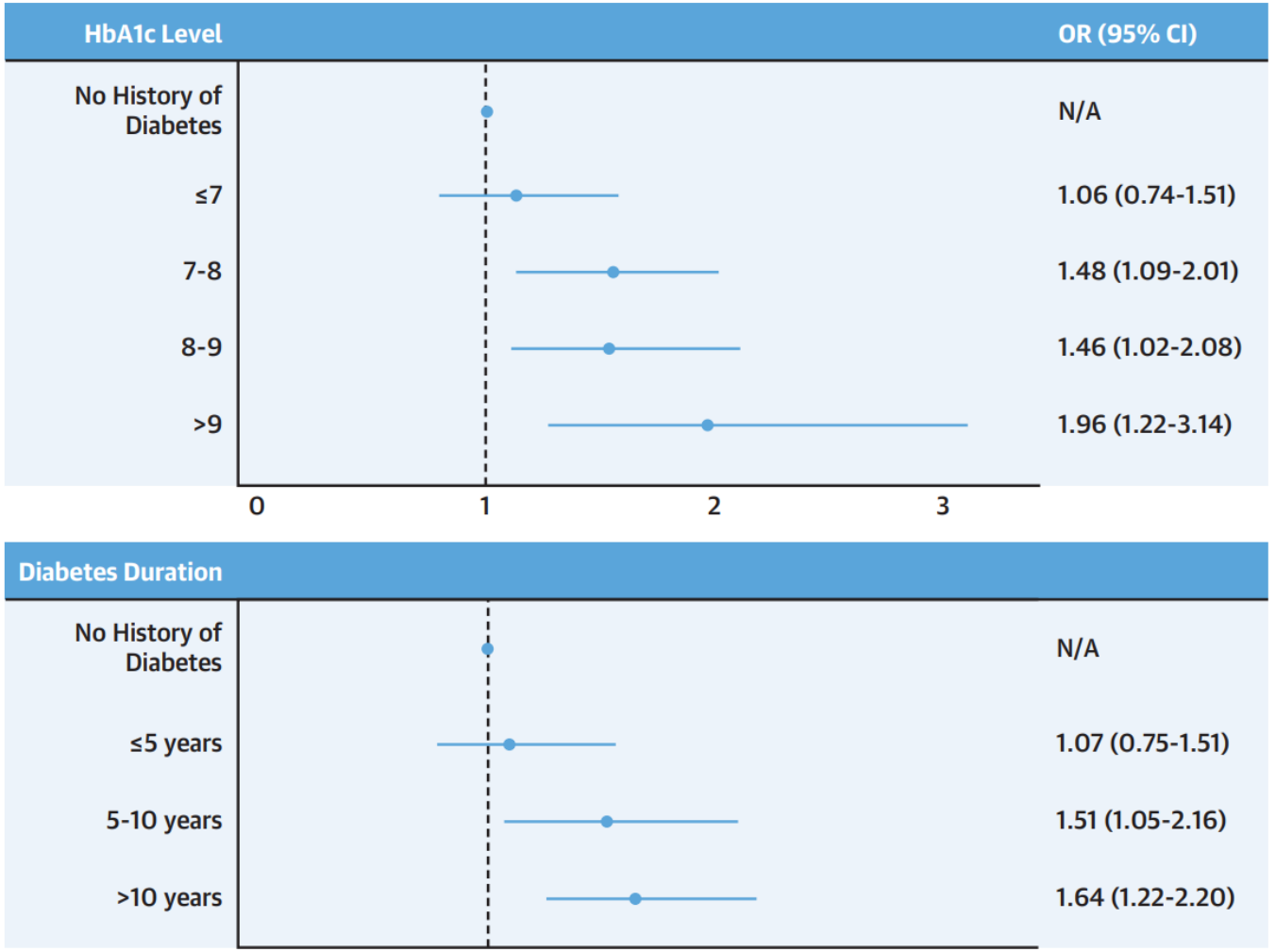
None of the authors have any conflicts of interest to declare.

Atrial fibrillation and diabetes

Table 1
Odd ratios and *p* values for diabetes mellitus (DM) correlation with atrial fibrillation, atrial flutter, coronary artery disease (CAD), congestive heart failure (CHF) and left ventricular hypertrophy (LVH)

	OR	95% CI	*p* value
Atrial fibrillation	2.13	2.10–2.16	< 0.0001
Atrial flutter	2.20	2.15–2.26	< 0.0001
CAD	2.39	2.34–2.44	< 0.0001
CHF	3.12	3.09–3.16	< 0.0001
LVH	1.85	1.77–1.92	< 0.0001

Atrial fibrillation and diabetes



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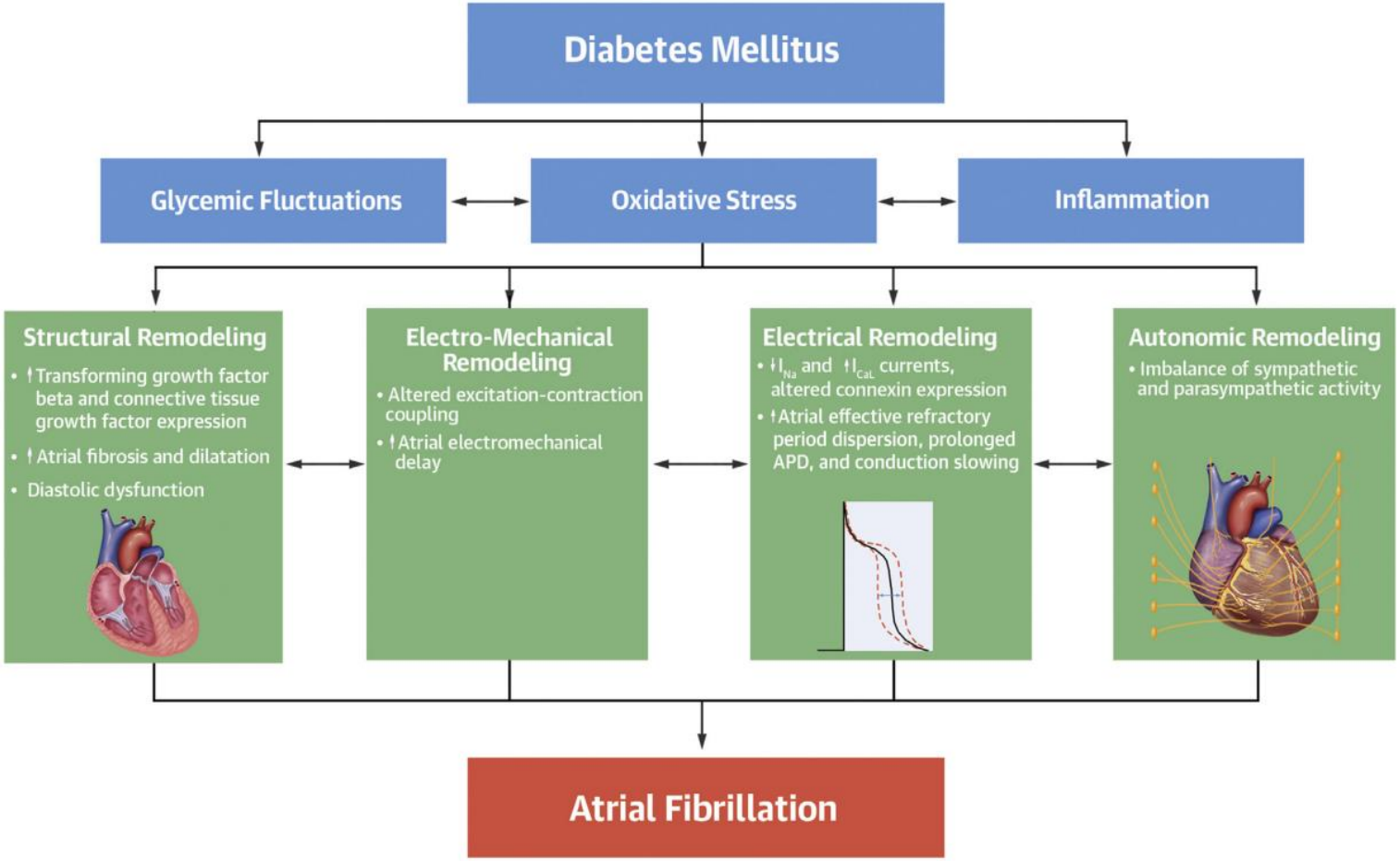
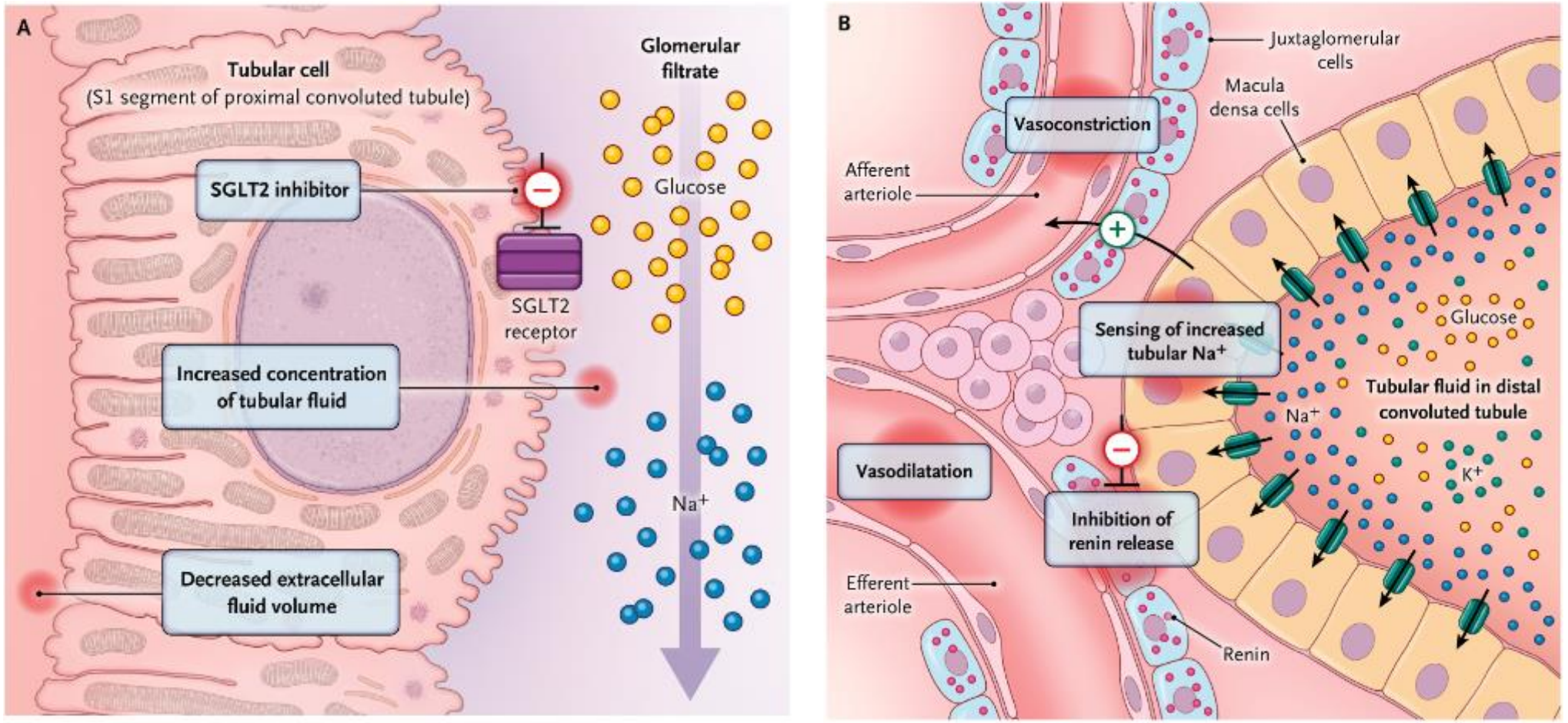
Atrial fibrillation and diabetes

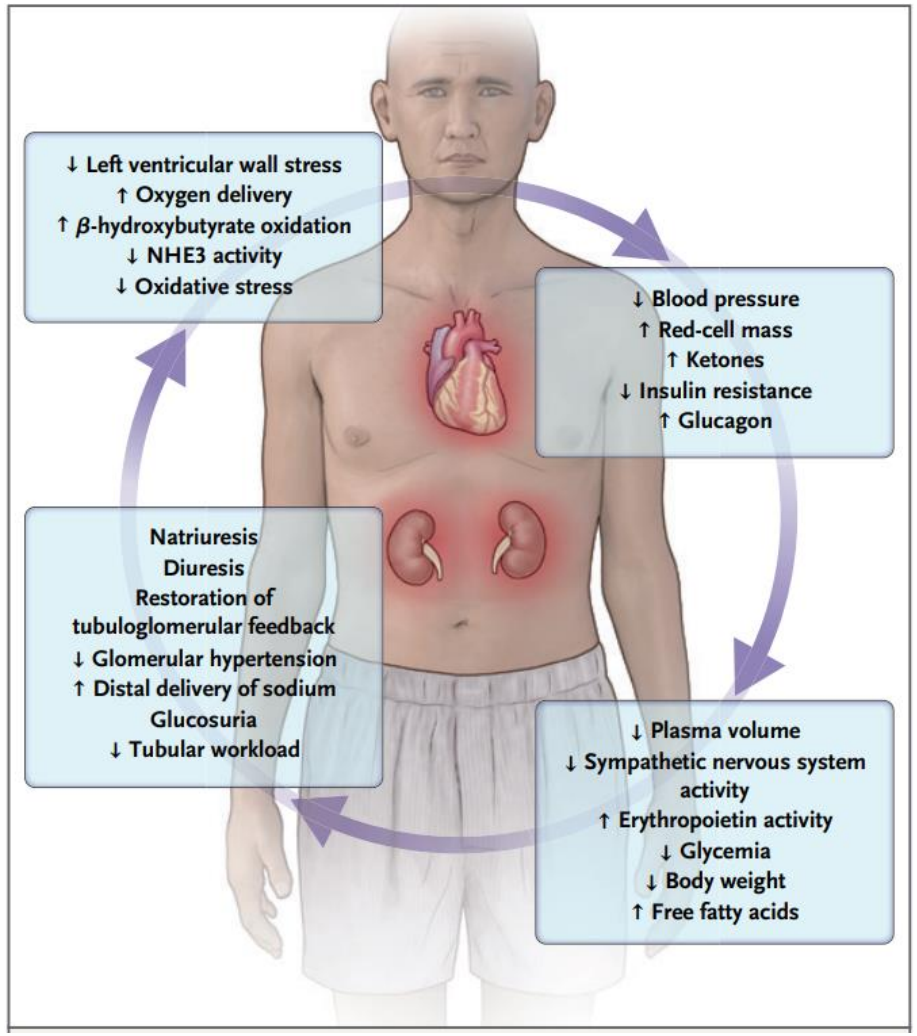


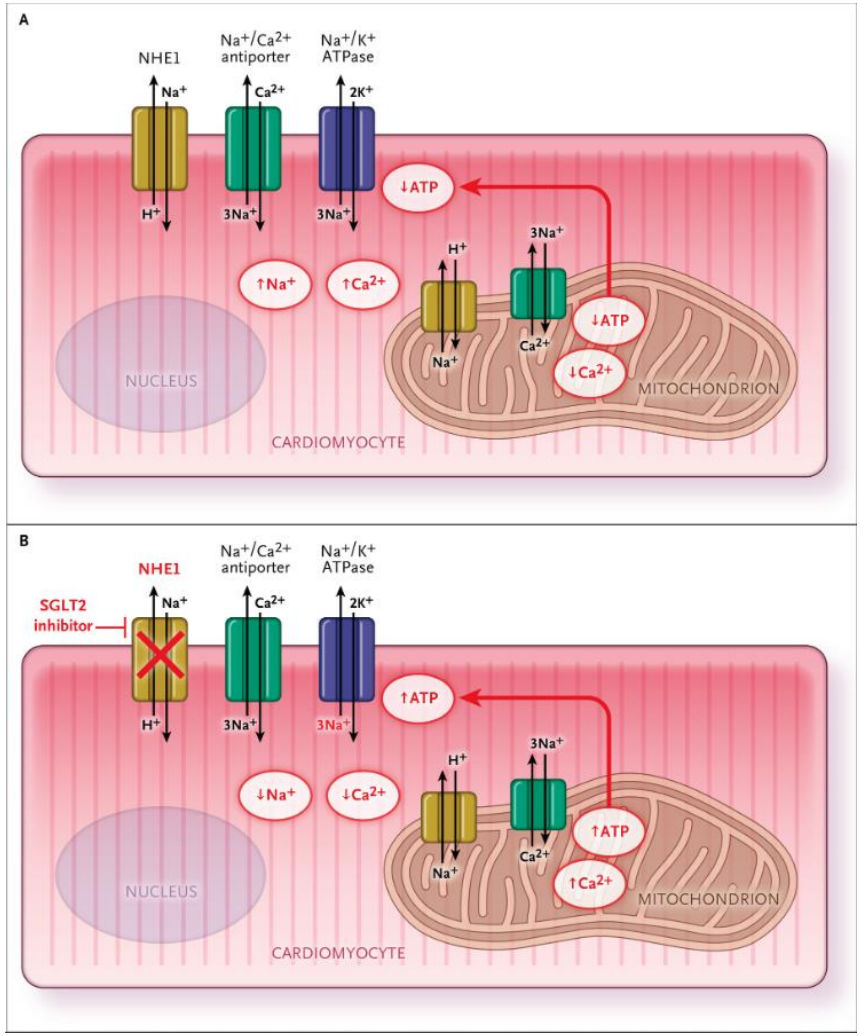
SGLT-2 inhibitor and cardiovascular disease



N Engl J Med (2022) 386:2024-2034

SGLT-2 inhibitor and cardiovascular disease





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SGLT-2 inhibitor and cardiovascular disease

	EMPA-REG	CANVAS	LEADER	SUSTAIN-6
Agent	Empagliflozin	Canagliflozin	Liraglutide	Semaglutide
n	7,020	10,142	9,340	3,297
Median follow-up, yrs	3.1	2.4	3.8	2.1
Mean baseline HbA_{1c}, %	8.1	8.2	8.7	8.7
Primary outcome	**CV death** Nonfatal MI Nonfatal stroke	CV death Nonfatal MI Nonfatal stroke	**CV death** Nonfatal MI Nonfatal stroke	CV death Nonfatal MI **Nonfatal stroke**
HR (95% CI)	**0.86** (0.74-0.99), p = 0.04	**0.86** (0.75-0.97), p = 0.02	**0.87** (0.78-0.97) p = 0.01	**0.74** (0.58-0.95) p = 0.02
Adverse events	Genital infections (male and female)	Amputations, fractures, male genital infections, female mycotic infections, volume depletion	Acute gallstone disease, injection site reactions, and adverse events leading to drug discontinuation (nausea, vomiting, diarrhea, abdominal pain/discomfort, anorexia)	Retinopathy, gastrointestinal disorders, any adverse leading to drug discontinuation (nausea, vomiting, diarrhea in a dose-dependent response)

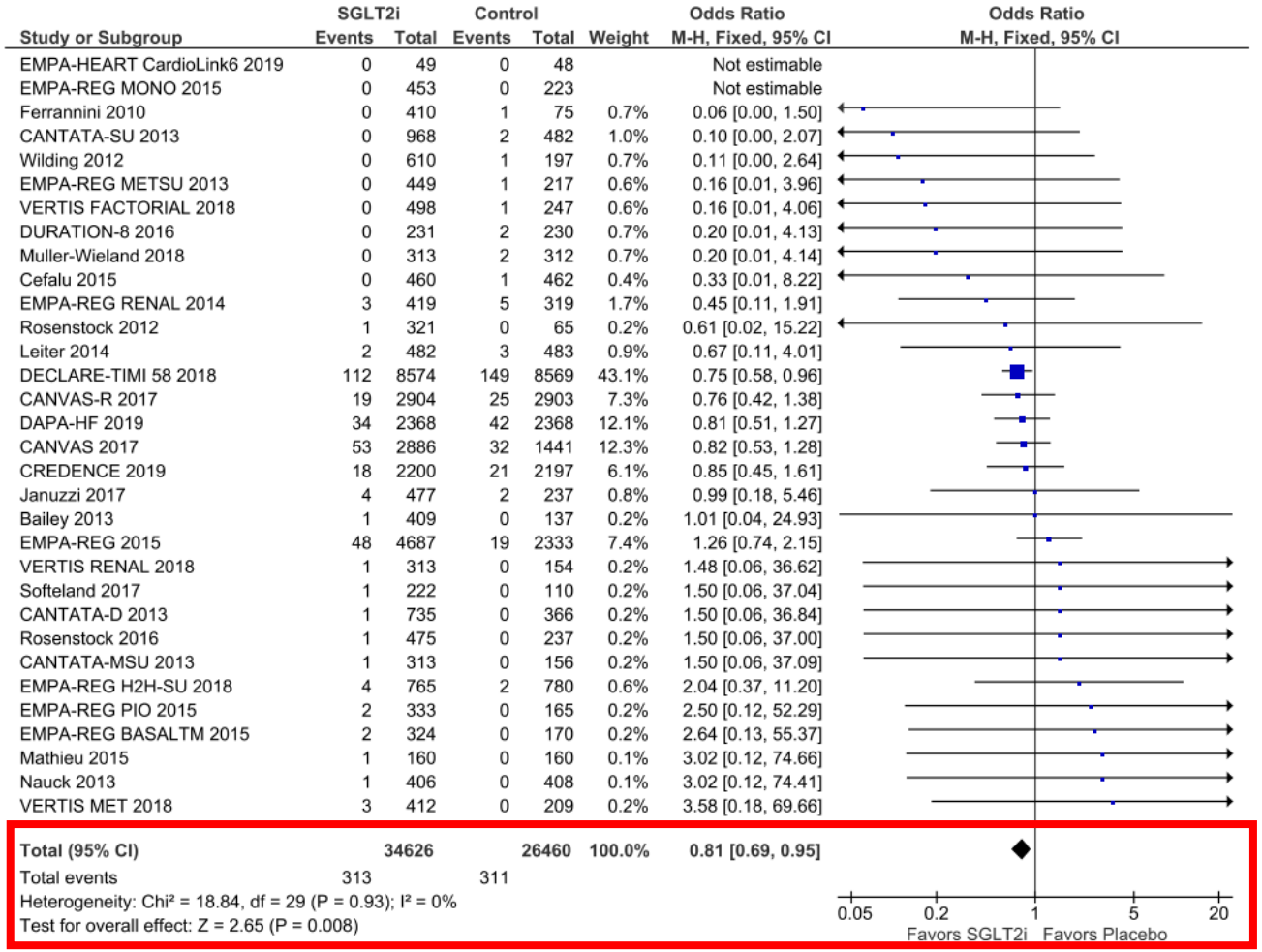
SGLT-2 inhibitor and cardiovascular disease

Table 2. Cardiovascular Outcome Trials Involving Patients with Heart Failure.*

Variable	DAPA-HF	EMPEROR-Reduced	EMPEROR-Preserved	SOLOIST-WHF
Drug	Dapagliflozin	Empagliflozin	Empagliflozin	Sotagliflozin
No. of patients	4744	3730	5988	1222
Type 2 diabetes — % of patients	41.7	49.8	49.1	100
LVEF — %	31.1	27.4	54.3	35
Median NT-proBNP — pg/ml	1437	1907	970	1864
Mean eGFR — ml/min/1.73 m^2	65.7	62.0	60.6	49.9
Outcomes — hazard ratio (95% CI)				
Cardiovascular death or hospitalization for heart failure	0.74 (0.65–0.85)	0.75 (0.68–0.86)	0.79 (0.69–0.90)	0.67 (0.52–0.85)
Hospitalization for heart failure	0.70 (0.59–0.83)	0.69 (0.59–0.81)	0.73 (0.61–0.88)	0.64 (0.49–0.83)

N Engl J Med (2022) 386:2024-2034

SGLT-2 inhibitor and atrial fibrillation



Study or Subgroup	SGLT2i Events	SGLT2i Total	Control Events	Control Total	Weight	Odds Ratio M-H, Fixed, 95% CI
EMPA-HEART CardioLink6 2019	0	49	0	48		Not estimable
EMPA-REG MONO 2015	0	453	0	223		Not estimable
Ferrannini 2010	0	410	1	75	0.7%	0.06 [0.00, 1.50]
CANTATA-SU 2013	0	968	2	482	1.0%	0.10 [0.00, 2.07]
Wilding 2012	0	610	1	197	0.7%	0.11 [0.00, 2.64]
EMPA-REG METSU 2013	0	449	1	217	0.6%	0.16 [0.01, 3.96]
VERTIS FACTORIAL 2018	0	498	1	247	0.6%	0.16 [0.01, 4.06]
DURATION-8 2016	0	231	2	230	0.7%	0.20 [0.01, 4.13]
Muller-Wieland 2018	0	313	2	312	0.7%	0.20 [0.01, 4.14]
Cefalu 2015	0	460	1	462	0.4%	0.33 [0.01, 8.22]
EMPA-REG RENAL 2014	3	419	5	319	1.7%	0.45 [0.11, 1.91]
Rosenstock 2012	1	321	0	65	0.2%	0.61 [0.02, 15.22]
Leiter 2014	2	482	3	483	0.9%	0.67 [0.11, 4.01]
DECLARE-TIMI 58 2018	112	8574	149	8569	43.1%	0.75 [0.58, 0.96]
CANVAS-R 2017	19	2904	25	2903	7.3%	0.76 [0.42, 1.38]
DAPA-HF 2019	34	2368	42	2368	12.1%	0.81 [0.51, 1.27]
CANVAS 2017	53	2886	32	1441	12.3%	0.82 [0.53, 1.28]
CREDENCE 2019	18	2200	21	2197	6.1%	0.85 [0.45, 1.61]
Januzzi 2017	4	477	2	237	0.8%	0.99 [0.18, 5.46]
Bailey 2013	1	409	0	137	0.2%	1.01 [0.04, 24.93]
EMPA-REG 2015	48	4687	19	2333	7.4%	1.26 [0.74, 2.15]
VERTIS RENAL 2018	1	313	0	154	0.2%	1.48 [0.06, 36.62]
Softeland 2017	1	222	0	110	0.2%	1.50 [0.06, 37.04]
CANTATA-D 2013	1	735	0	366	0.2%	1.50 [0.06, 36.84]
Rosenstock 2016	1	475	0	237	0.2%	1.50 [0.06, 37.00]
CANTATA-MSU 2013	1	313	0	156	0.2%	1.50 [0.06, 37.09]
EMPA-REG H2H-SU 2018	4	765	2	780	0.6%	2.04 [0.37, 11.20]
EMPA-REG PIO 2015	2	333	0	165	0.2%	2.50 [0.12, 52.29]
EMPA-REG BASALTM 2015	2	324	0	170	0.2%	2.64 [0.13, 55.37]
Mathieu 2015	1	160	0	160	0.1%	3.02 [0.12, 74.66]
Nauck 2013	1	406	0	408	0.1%	3.02 [0.12, 74.41]
VERTIS MET 2018	3	412	0	209	0.2%	3.58 [0.18, 69.66]
Total (95% CI)		**34626**		**26460**	**100.0%**	**0.81 [0.69, 0.95]**
Total events	313		311			

Heterogeneity: Chi² = 18.84, df = 29 (P = 0.93); I² = 0%
Test for overall effect: Z = 2.65 (P = 0.008)

Figure 2 Incident atrial arrhythmias with sodium-glucose cotransporter 2 inhibitors (SGLT2is) vs control in patients with diabetes or heart failure. Summary statistic favors SGLT2is (odds ratio 0.81; 95% confidence interval [CI] 0.69–0.95; $P = .008$) with a significant reduction in incident atrial fibrillation or flutter compared with placebo or active control. M-H = Mantel-Haenszel.

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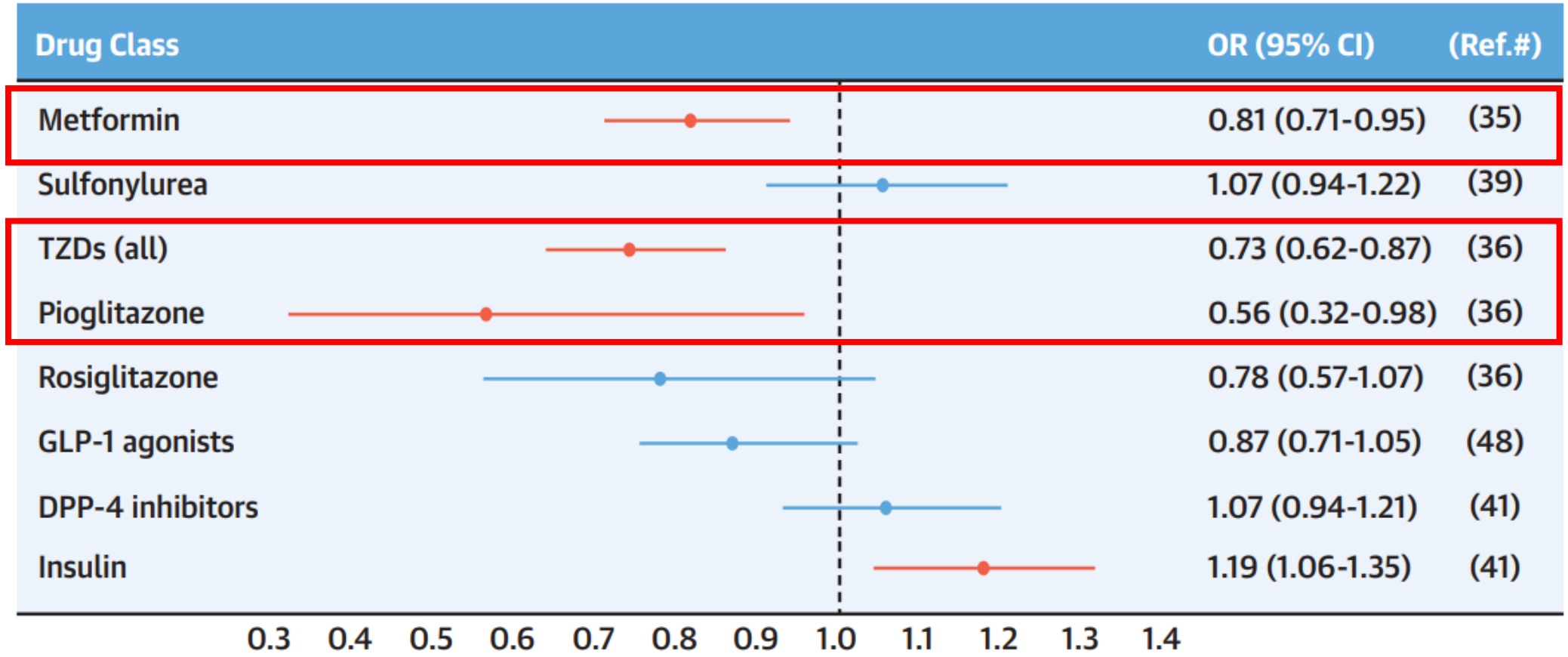
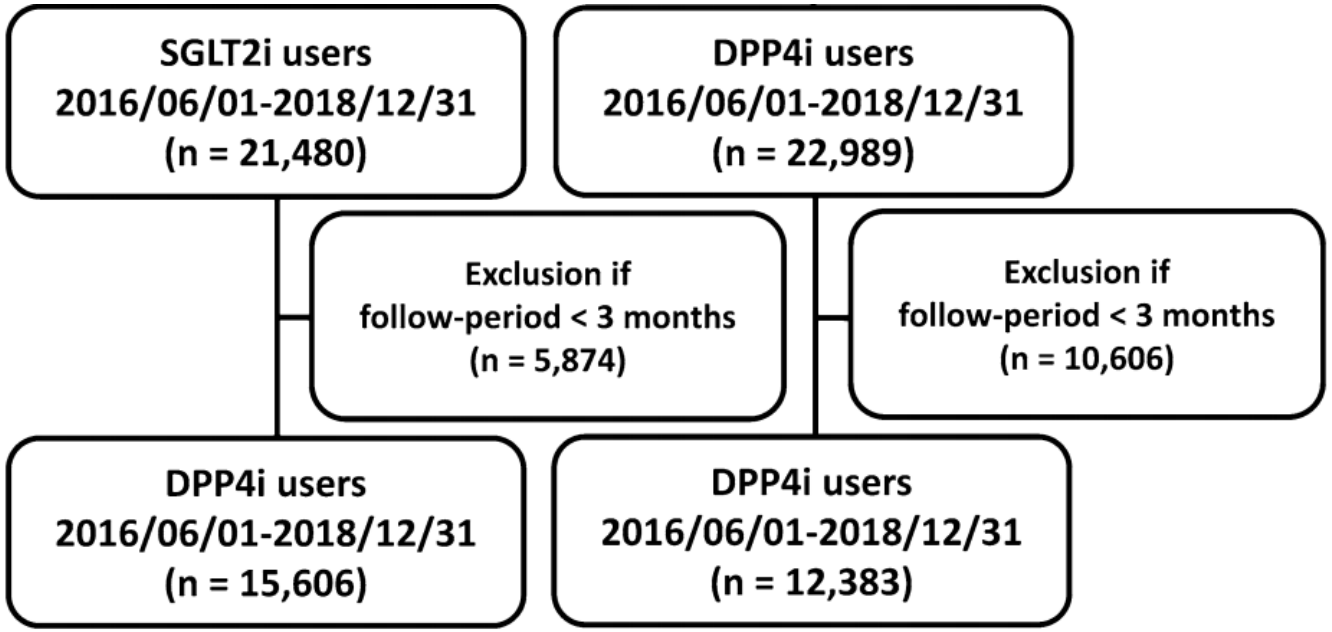
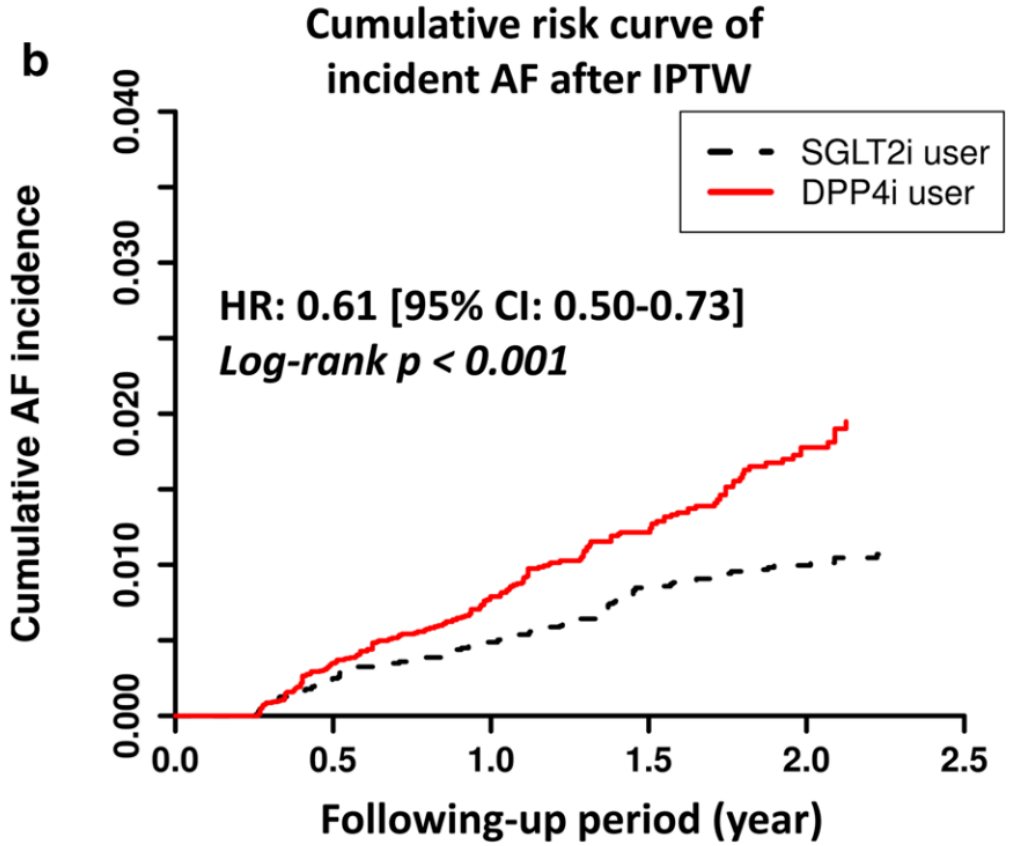
SGLT-2 inhibitor and atrial fibrillation



SGLT-2 inhibitor VS DPP-4 inhibitor on atrial fibrillation





Cardiovasc Diabetol (2020) 19:188

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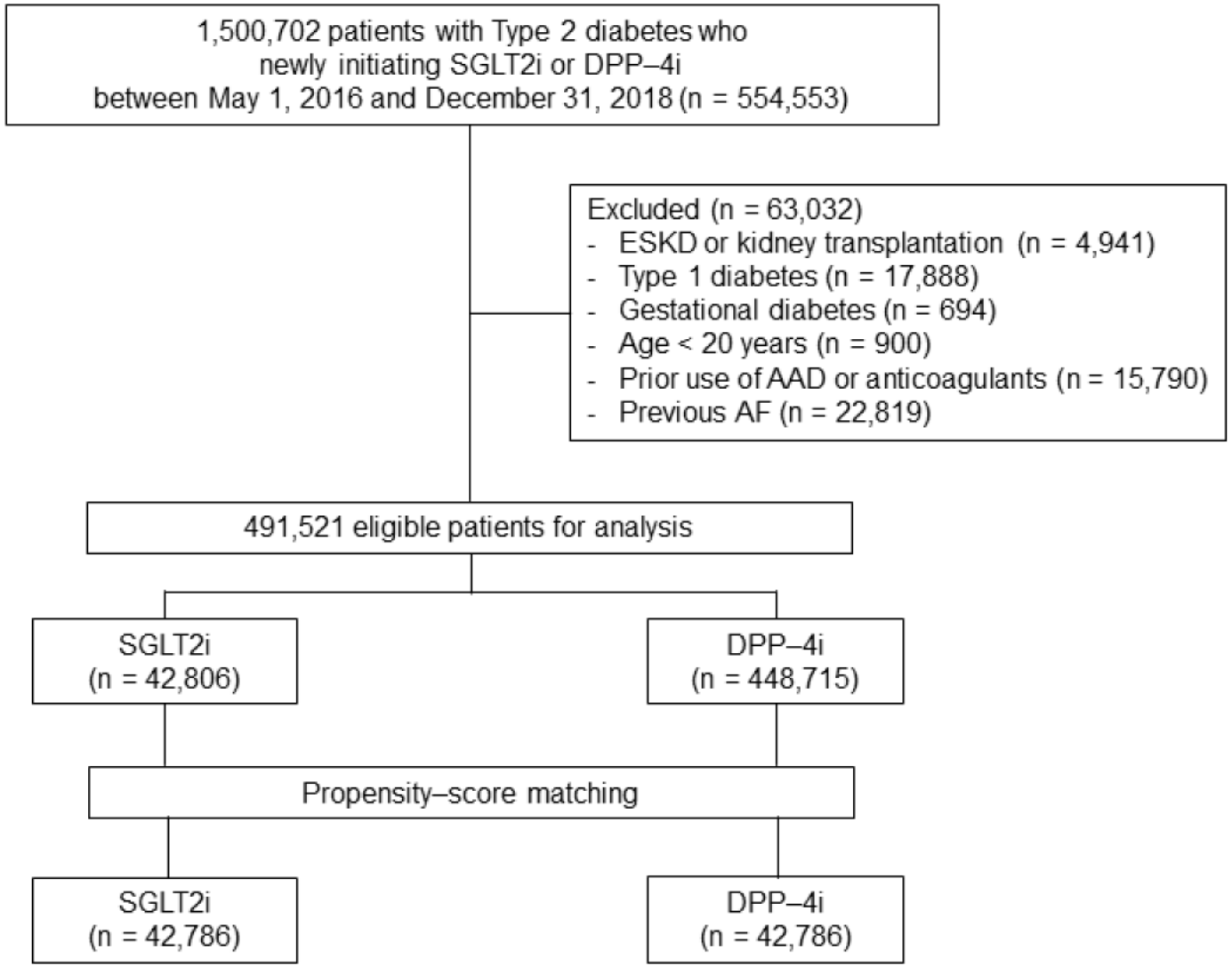
Methods

- NHIS database
- 2016.05.01~2018.12.31
- Newly initiating
- AF : discharge diagnosis or confirmed more than twice in the outpatient visits



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Methods

- Considered 110 potential confounders including sex, age, household income, complications, comorbidities, other glucose-lowering drugs
- Propensity score-matched analysis was performed
- On-treatment and intention-to-treat analysis

Results

	N	%
SGLT2i	42,230	100.0
Dapagliflozin	22,915	54.3
Empagliflozin	16,566	39.2
Ipragliflozin	2,749	6.5
DPP-4i	42,230	100.0
Alogliptin	3,259	7.7
Anagliptin	1,543	3.7
Evogliptin	1,807	4.3
Gemigliptin	8,571	20.3
Linagliptin	8,870	21.0
Saxagliptin	2,019	4.8
Sitagliptin	9,364	22.2
Teneligliptin	4,327	10.2
Vildagliptin	2,470	5.8

Results

Table 2. Hazard ratios of atrial fibrillation events associated with SGLT2i use versus DPP–4i use (reference) in the propensity score–matched cohort

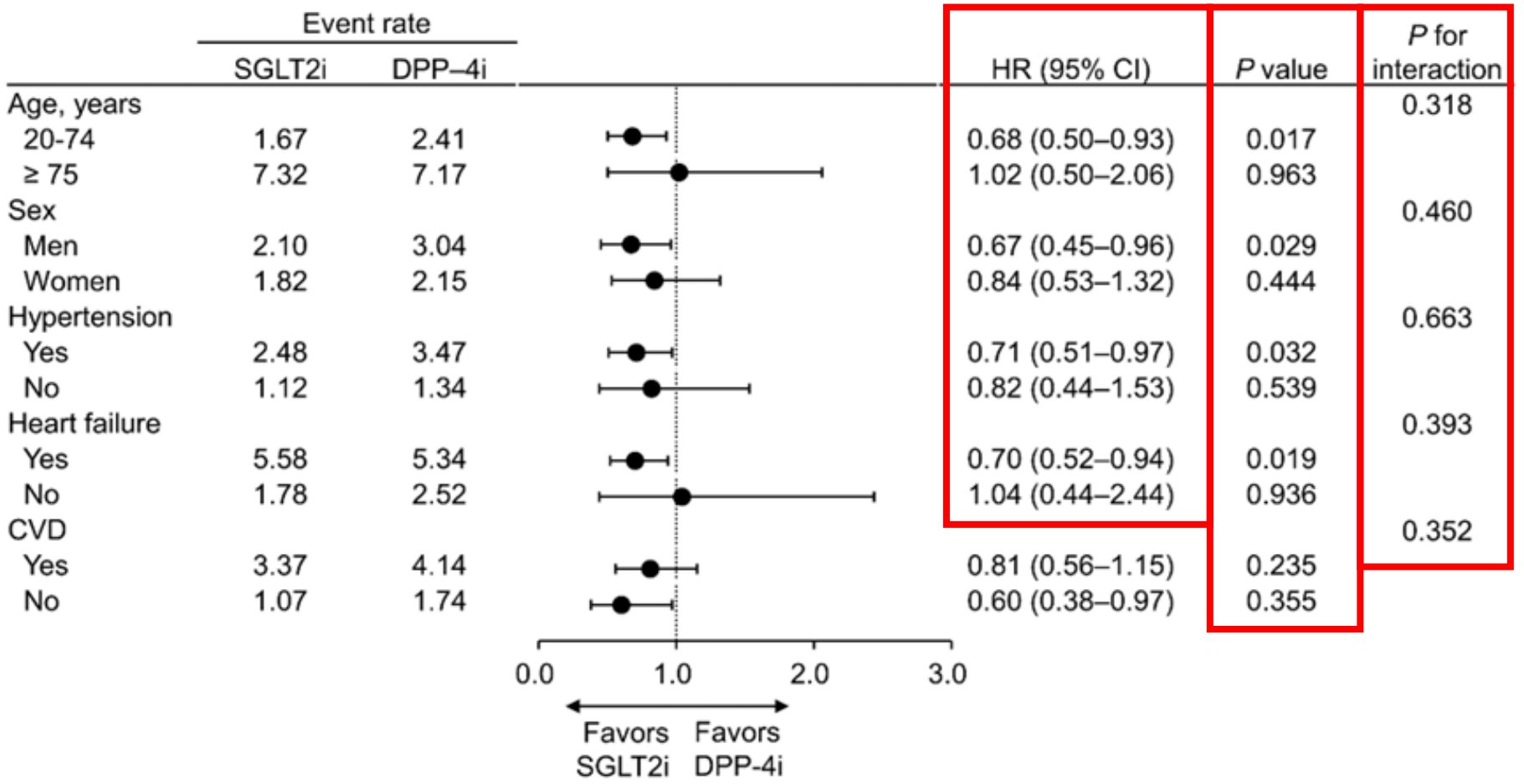
	SGLT2i (n=42,786)			DPP–4i (n=42,786)					
Type of analysis	Total follow–up years	No. of events	Event rate	Total follow–up years	No. of events	Event rate	Absolute event rate difference	HR (95% CI)	*P* value
OT	44,013	86	1.95	40,744	108	2.65	−0.7 (−1.3 to −0.1)	0.73 (0.55–0.97)	0.028
ITT	56,014	147	2.62	55,615	176	3.17	−0.5 (−1.2 to −0.1)	0.83 (0.66–1.03)	0.092

Event rates were estimated per 1,000 person–years.

CI, confidence interval; DPP–4i, dipeptidyl peptidase–4 inhibitor; HR, hazard ratio; ITT, intention–to–treat; SGLT2i, sodium–glucose cotransporter 2 inhibitor; OT, on–treatment

Results

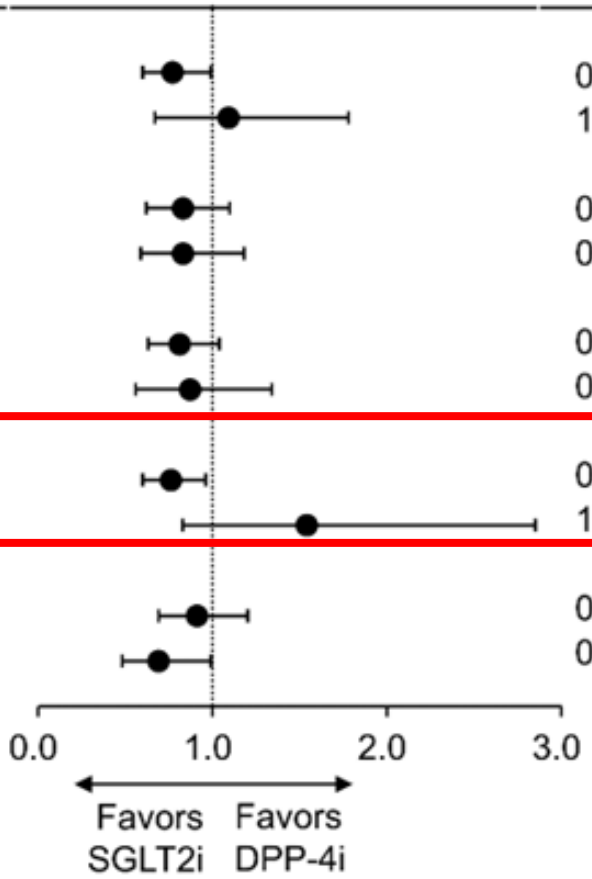
A. On−treatment



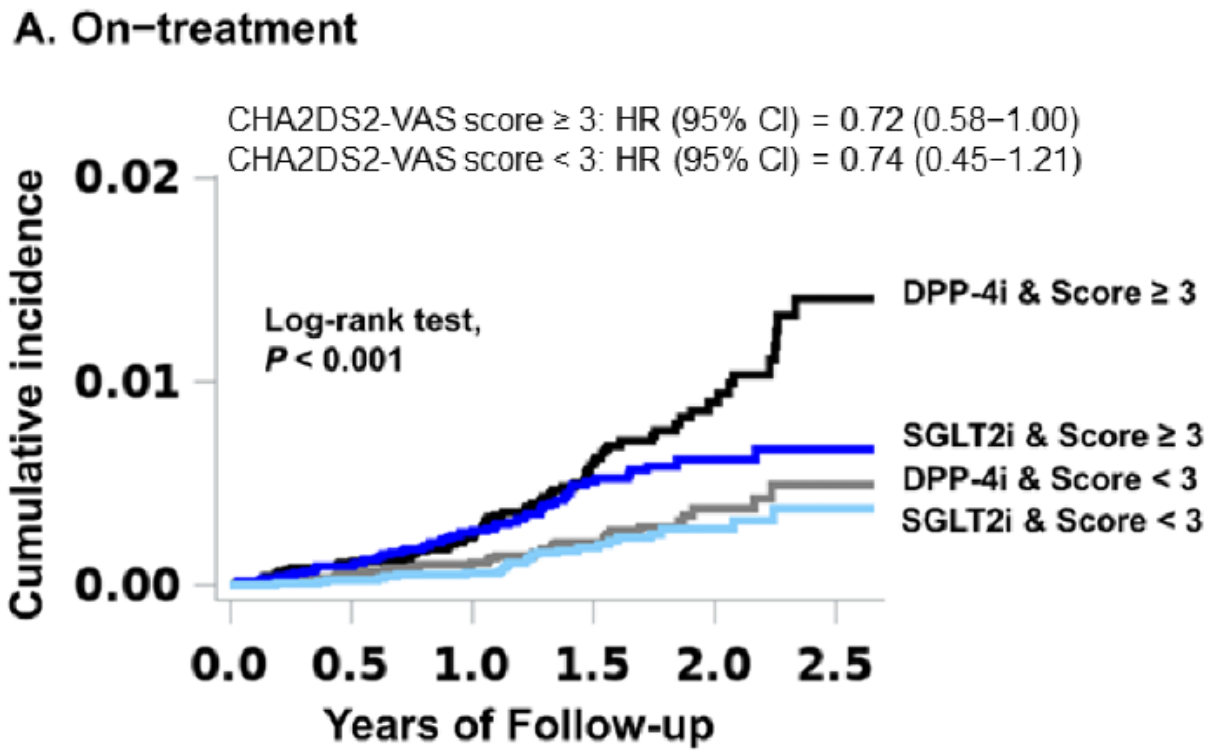
Results

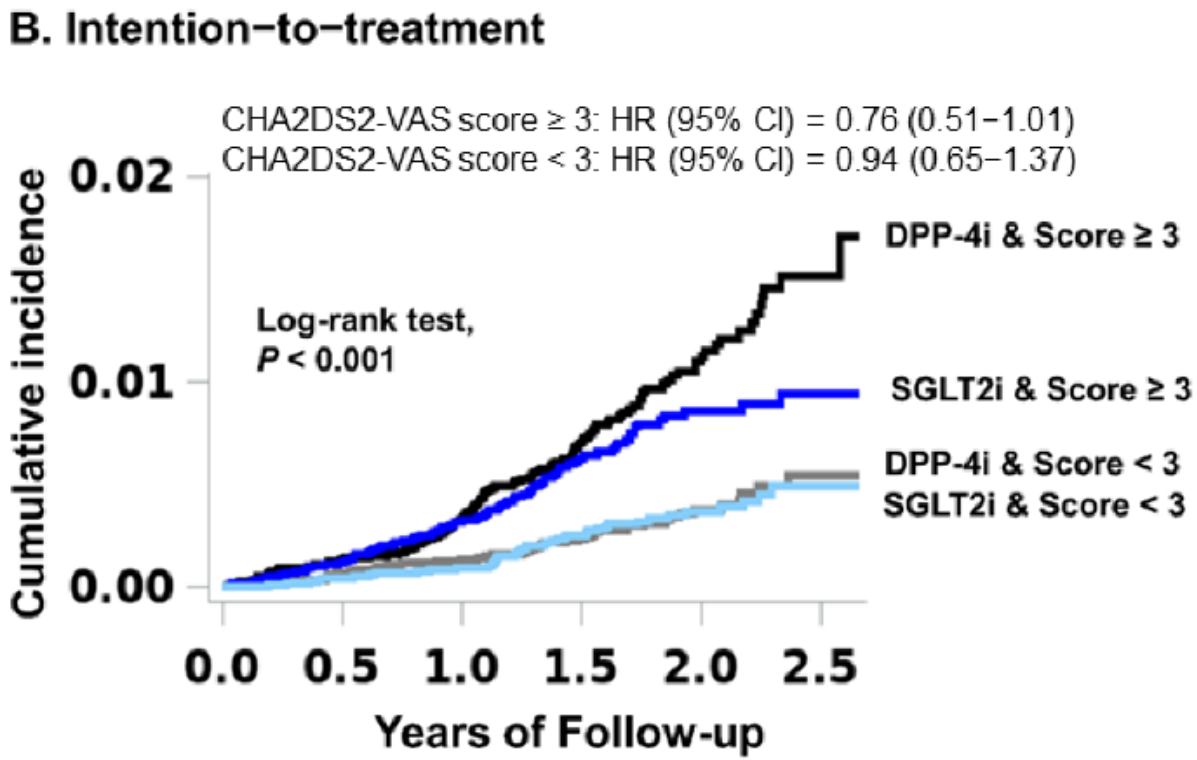
B. Intention−to−treatment

	Event rate			*P* value	*P* for interaction
	SGLT2i	DPP–4i	HR (95% CI)		
Age, years					0.209
20-74	2.13	2.75	0.77 (0.60–0.99)	0.039	
≥ 75	11.67	10.69	1.09 (0.67–1.78)	0.721	
Sex					0.965
Men	2.74	3.33	0.83 (0.62–1.10)	0.185	
Women	2.42	2.94	0.83 (0.59–1.18)	0.299	
Hypertension					0.774
Yes	3.33	4.10	0.81 (0.63–1.04)	0.102	
No	1.63	1.88	0.87 (0.56–1.34)	0.530	
Heart failure					0.036
Yes	10.47	6.88	0.76 (0.60–0.96)	0.022	
No	2.28	2.99	1.54 (0.83–2.85)	0.171	
CVD					0.238
Yes	4.58	5.01	0.91 (0.69–1.20)	0.513	
No	1.45	2.10	0.69 (0.48–0.99)	0.044	



Results


A. On−treatment
CHA2DS2-VAS score ≥ 3: HR (95% CI) = 0.72 (0.58−1.00)
CHA2DS2-VAS score < 3: HR (95% CI) = 0.74 (0.45−1.21)
Cumulative incidence
0.02
0.01
0.00
Log-rank test,
P < 0.001
DPP-4i & Score ≥ 3
SGLT2i & Score ≥ 3
DPP-4i & Score < 3
SGLT2i & Score < 3
0.0 0.5 1.0 1.5 2.0 2.5
Years of Follow-up


B. Intention−to−treatment
CHA2DS2-VAS score ≥ 3: HR (95% CI) = 0.76 (0.51−1.01)
CHA2DS2-VAS score < 3: HR (95% CI) = 0.94 (0.65−1.37)
Cumulative incidence
0.02
0.01
0.00
Log-rank test,
P < 0.001
DPP-4i & Score ≥ 3
SGLT2i & Score ≥ 3
DPP-4i & Score < 3
SGLT2i & Score < 3
0.0 0.5 1.0 1.5 2.0 2.5
Years of Follow-up

Discussion

- SGLT2i use was associated with a reduced incidence of AF, especially in individuals with HF or a higher thromboembolic risk.

Discussion

- The incidence of AF is higher in individuals with type 2 diabetes than in the general population.
- Metformin and pioglitazone may be associated with a lower long–term risk of AF in individuals with diabetes.
- About DPP–4i, clear evidence is still lacking.
- SGLT2i have favorable pleiotropic effects on type 2 diabetes, chronic kidney disease, and HF.

Limitations

- Accuracy of diagnoses
- Retrospective studies cannot demonstrate causal relationships.
- The median follow–up duration was 1.3 years.
- Further studies are needed to determine whether SGLT2i reduce the risk of AF, in individuals without diabetes but with recently developed HF with preserved ejection fraction.

Conclusion

Initiating an SGLT2i for the treatment of type 2 diabetes had a greater benefit in terms of AF prevention than initiating a DPP–4i in South Korea. This benefit was more pronounced in individuals with HF or a high thromboembolic risk


Thank You