

Comparative Effectiveness of Second-Line Antidiabetic Medications on the Risk of Major Adverse Cardiovascular Events: A Real-World Study in China

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BACKGROUND

- ✓ China has the world’s largest diabetes population (>140 million adults, 12.4% prevalence), with cardiovascular disease accounting for over half of diabetes-related deaths.
- ✓ After metformin, second-line choices vary across antidiabetic medications (ADMs) classes. Evidence on their cardiovascular effects varies across drug classes, with newer agents (GLP-1 RAs, SGLT-2is, DPP-4is) generally showing more favorable outcomes than older ones.
- ✓ **Evidence gap:**
 - Cardiovascular Outcome Trials (CVOTs) have shown cardioprotective benefits for GLP-1 RAs and SGLT-2is, neutral effects for DPP-4is, and potential risks for older agents like sulfonylureas, but these trials were largely conducted in high-risk, controlled populations.
 - Few studies have compared all major second-line ADMs in the real-world early intensification stage after metformin monotherapy.

AIMS

To evaluate the comparative effectiveness of second-line ADMs on the risk of major adverse cardiovascular events (MACE) in patients with type 2 diabetes (T2DM).

METHODS

STUDY DESIGN

A retrospective cohort study using electronic medical records from a large healthcare platform in Eastern China was conducted. The index date was defined as the date of the first prescription of the index ADM.

POPULATION

Inclusion Criteria:

- Adult patients (≥18 years) initiating one of the second-line ADMs
- At least two outpatient or one inpatient diagnosis of T2DM within the 12 months before and up to 3 months after the index ADM
- Continuous enrollment in the database for at least 12 months prior to the index date (baseline period)
- Date of Admission: January 1, 2018 to October 31, 2024

Exclusion Criteria:

- Diagnosis of type 1 diabetes mellitus or gestational diabetes
- more than 1 ADM class prescription filled on the index date

COVARIATES

Baseline covariates included demographics, HbA1c category, comorbidities (e.g., hypertension, CVD, obesity, nephropathy), endocrinology visits and prior metformin use.

OUTCOME

The outcome was the first occurrence of major adverse cardiovascular events (MACE), defined as a composite of nonfatal stroke, nonfatal myocardial infarction, or all-cause mortality.

STATISTICAL ANALYSIS

Cox proportional hazards models were used to estimate the risk of MACE. Intention-to-treat (ITT) analysis: treatment groups were defined based on the initial prescribed ADM at baseline, regardless of subsequent treatment changes or discontinuation. Per-protocol (PP) analysis: included only patients who maintained use of the same ADM throughout follow-up, reflecting treatment adherence.

RESULTS

- ✓ Distribution: GLP-1 RA (n=17,416), SGLT-2i (n=19,863), DPP-4i (n=6,880), Insulin (n=41,349), SU (n=21,549), AGI (n=8,214), TZD (n=1,029), Meglitinides (n=3,510)
- ✓ Key differences in baseline characteristics (Table 1):
 - GLP-1 RA: youngest (mean age 54.5 yrs), highest dyslipidemia (32.4%) and obesity (12.3%).
 - SGLT-2i: highest heart failure (14.0%) and myocardial infarction (6.8%).
 - AGI: highest stroke prevalence (45.0%).
 - Insulin: poorest glycemic control (HbA1c >10%, 20.9%).
 - SU: most prior metformin users (58.9%).

Table 1 Characteristics of the study population

Characteristic	GLP-1 RA, N=17416	SGLT-2 i, N=19863	DPP-4 i, N=6880	Insulin, N=41349	SU, N=21549	AGI, N=8214	TZD, N=1029	Meglitinide, N=3510	P-value
Age, mean (SD)	54.51 (14.67)	61.86 (13.12)	63.24 (12.60)	64.38 (13.39)	66.67 (11.00)	67.20 (12.15)	63.39 (12.63)	68.16 (11.51)	<0.001
Female, n (%)	7367 (42.3)	7579 (38.2)	3309 (48.1)	18519 (44.8)	11185 (51.9)	3760 (45.8)	540 (52.5)	1749 (49.8)	<0.001
Payment, n (%)									<0.001
UEBMI	11116 (63.8)	11294 (56.9)	4339 (63.1)	20567 (49.7)	10143 (47.1)	4400 (53.6)	545 (53.0)	1771 (50.5)	
URRBMI	2130 (12.2)	3623 (18.2)	1012 (14.7)	9634 (23.3)	6743 (31.3)	1868 (22.7)	271 (26.3)	895 (25.5)	
Other	3507 (20.1)	4051 (20.4)	1249 (18.2)	9202 (22.3)	3322 (15.4)	1602 (19.5)	166 (16.1)	656 (18.7)	
OOP	663 (3.8)	895 (4.5)	280 (4.1)	1946 (4.7)	1341 (6.2)	344 (4.2)	47 (4.6)	188 (5.4)	
HbA1c, n (%)									<0.001
Result not available	8879 (51.0)	9388 (47.3)	3285 (47.7)	21603 (52.2)	15872 (73.7)	3879 (47.2)	745 (72.4)	2107 (60.0)	
<8	3585 (20.6)	5661 (28.5)	2170 (31.5)	5507 (13.3)	3113 (14.4)	2611 (31.8)	177 (17.2)	814 (23.2)	
8-10	2653 (15.2)	3100 (15.6)	964 (14.0)	5586 (13.5)	1658 (7.7)	1083 (13.2)	72 (7.0)	393 (11.2)	
>10	2299 (13.2)	1714 (8.6)	461 (6.7)	8652 (20.9)	906 (4.2)	641 (7.8)	35 (3.4)	196 (5.6)	
Comorbid conditions, n (%)									
Hypertension	11264 (64.7)	13866 (69.8)	4300 (62.5)	24801 (60.0)	14196 (65.9)	5905 (71.9)	636 (61.8)	2471 (70.4)	<0.001
Dyslipidemia	5640 (32.4)	4599 (23.2)	1363 (19.8)	5287 (12.8)	2705 (12.6)	1437 (17.5)	147 (14.3)	448 (12.8)	<0.001
Obesity	2142 (12.3)	325 (1.6)	48 (0.7)	248 (0.6)	58 (0.3)	34 (0.4)	6 (0.6)	7 (0.2)	<0.001
Heart failure	1074 (6.2)	2786 (14.0)	359 (5.2)	3141 (7.6)	1154 (5.4)	758 (9.2)	43 (4.2)	322 (9.2)	<0.001
Myocardial infarction	524 (3.0)	1349 (6.8)	145 (2.1)	1030 (2.5)	424 (2.0)	258 (3.1)	20 (1.9)	86 (2.5)	<0.001
Stroke	5156 (29.6)	6131 (30.9)	2028 (29.5)	12021 (29.1)	6372 (29.6)	3696 (45.0)	267 (25.9)	1247 (35.5)	<0.001
Nephropathy	5911 (33.9)	7853 (39.5)	1887 (27.4)	10194 (24.7)	5293 (24.6)	3099 (37.7)	226 (22.0)	1111 (31.7)	<0.001
Coronary atherosclerosis	2266 (13.0)	1591 (8.0)	513 (7.5)	4171 (10.1)	741 (3.4)	498 (6.1)	41 (4.0)	376 (10.7)	<0.001
Diabetic neuropathy	2180 (12.5)	689 (3.5)	323 (4.7)	3265 (7.9)	463 (2.1)	371 (4.5)	29 (2.8)	105 (3.0)	<0.001
Diabetic retinopathy	1762 (10.1)	787 (4.0)	286 (4.2)	3370 (8.2)	638 (3.0)	378 (4.6)	36 (3.5)	123 (3.5)	<0.001
Number of endocrinologist visits, mean (SD)	2.91 (3.68)	0.85 (1.47)	1.42 (1.96)	0.85 (1.62)	0.36 (1.15)	0.78 (1.87)	0.61 (1.35)	0.50 (1.30)	<0.001
Metformin use, n (%)	3850 (22.1)	9198 (46.3)	3069 (44.6)	5386 (13.0)	12695 (58.9)	3551 (43.2)	573 (55.7)	1617 (46.1)	<0.001

➤ Intention-to- treat (ITT) analysis (Figure 1):

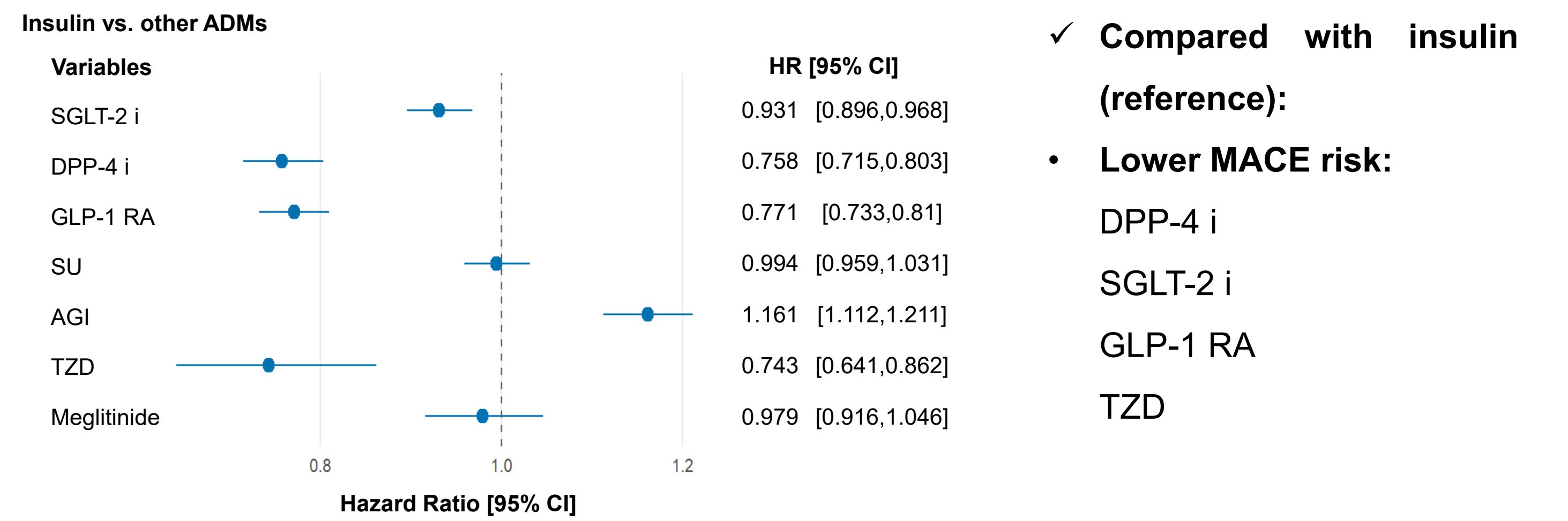


Figure 1: Hazard ratios for major adverse cardiovascular events in ITT analysis

➤ Per-protocol (PP) analysis (Figure 2):

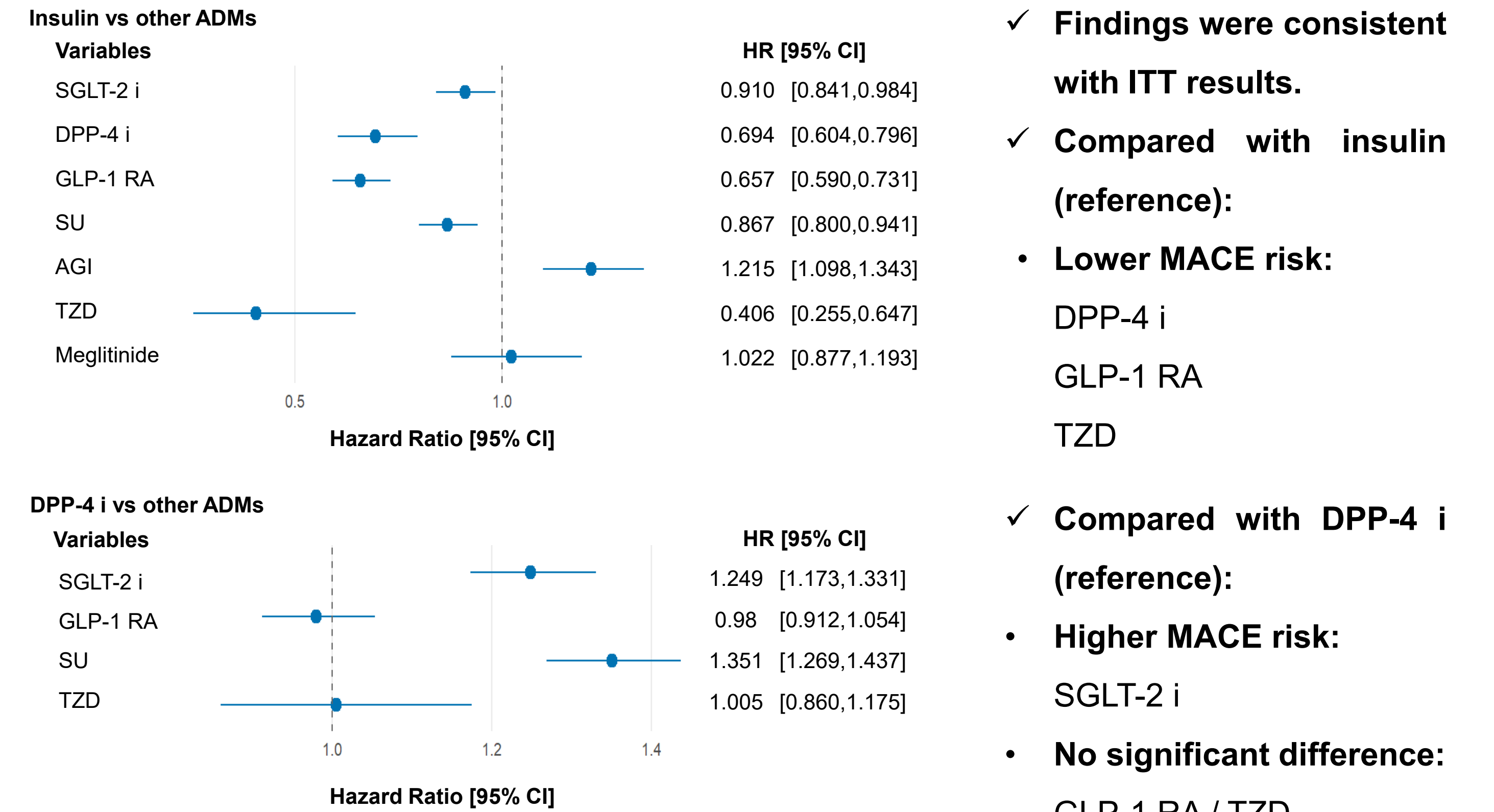


Figure 2: Hazard ratios for major adverse cardiovascular events in PP analysis

CONCLUSIONS

In this real-world study, SGLT-2 inhibitors, DPP-4 inhibitors, GLP-1 receptor agonists, and thiazolidinediones were associated with lower MACE risk, whereas α -glucosidase inhibitors showed a higher risk compared with insulin. GLP-1 receptor agonists and thiazolidinediones demonstrated similar MACE risks to DPP-4 inhibitors but lower risks compared with SGLT-2 inhibitors.

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Disclose

All authors of this presentation have nothing to disclose concerning possible or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.

