Cardiovascular Diabetology

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Comparative effectiveness of angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers on cardiovascular outcomes in older adults with type 2 diabetes mellitus: a target trial emulation study

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Abstract

Background Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are both recommended as first-line antihypertensive agents for patients with diabetes. While pharmacological mechanisms suggest that ACEIs may provide better cardiovascular protection than ARBs, this potential benefit has not been fully established in previous observational studies of patients with diabetes.

Methods An active-comparator new-user design within target trial emulation framework was implemented using Yinzhou Regional Health Care Database (YRHCD). We compared risks of major cardiovascular events (MACE) between older patients (age ≥ 65 years) with type 2 diabetes mellitus (T2DM) newly exposed to ACEIs and ARBs from January 1, 2010 to May 31, 2023. The primary outcomes were 3-point MACE, including hospitalized myocardial infarction, hospitalized stroke, and all-cause mortality (a proxy for cardiovascular mortality). We also assessed 4-point MACE, which further included hospitalized heart failure. Propensity scores were calculated to balance 44 identified confounders. Marginal structure models were applied to estimate per-protocol hazard ratios.

Results A total of 18,558 individuals were included, with 1,641 initiating ACEIs and 16,917 initiating ARBs. Their median age was 72 years and 45% were male. The adjusted hazard ratio for ACEIs vs. ARBs was 0.86 (95% confidence interval [CI], 0.68–1.10) for 3-point MACE and 0.83 (95% CI 0.69–0.99) for 4-point MACE. The 1-year absolute risk differences were − 0.30% (95% CI − 1.80–1.21%) for 3-point MACE and − 1.16% (95% CI − 2.97–0.66%) for 4-point MACE. Results were consistent across subgroup analyses (stratified by age, sex, as well as baseline major atherosclerotic cardiovascular disease, heart failure, other antihypertensive therapy, insulin therapy, and calendar year) and sensitivity analyses.

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Conclusions Among older patients with T2DM, the initiation of ACEIs was associated with a trend toward lower risk of MACE compared to ARBs, implying the potential cardiovascular benefits of ACEIs in this population.

Keywords Type 2 diabetes mellitus, Older, Angiotensin-converting enzyme inhibitors, Angiotensin II receptor blockers, Major cardiovascular events.

Research insights

What is currently known about this topic?

- Older adults with type 2 diabetes mellitus face high cardiovascular complications. Blood pressure control is a key strategy to reduce this risk. ACEIs and ARBs are both recommended as first-line antihypertensive therapies.

What is the key research question?

- Is there a difference in the efficacy between ACEIs and ARBs in reducing cardiovascular risk among older patients with type 2 diabetes mellitus?

What is new?

- This study employs an active-comparator, new-user design within the target trial emulation framework to evaluate the cardiovascular outcome of ACEIs' relative to ARBs in Chinese older adults with type 2 diabetes. The findings indicate that initiating ACEIs is associated with a trend toward lower risk of major cardiovascular events compared to ARBs.

How might this study influence clinical practice?

- The findings may support healthcare professionals in China should be cautious to prioritize ARBs over ACEIs for older adults with type 2 diabetes mellitus, potentially informing treatment guidelines and prescribing practices.

Background

Type 2 diabetes mellitus (T2DM) affects approximately 828 million individuals globally [1] and is rising in prevalence. In China alone, 18.8% of older adults (age ≥ 65 years) had T2DM in 2018, equating to 38 million individuals [2]. Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality in T2DM, accounting for 34.8% of case and nearly 70% of diabetes-related deaths, with older patients at even higher risk due to aging, comorbidities, and long-standing diabetes [3–5]. As global populations age, optimizing cardiovascular risk management for older adults with T2DM is increasingly critical.

Effective blood pressure control is essential for reducing cardiovascular risk in patients with diabetes. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are first-line antihypertensive agents, both recommended for their cardiovascular benefit. However, current clinical guidelines do not generally prioritize one over the other [6, 7]. ACEIs and ARBs both work by lowering the effects of angiotensin (Ang) II in the body, but they do so through distinct mechanisms: ACEIs inhibit angiotensin-converting enzyme to block the conversion from Ang I to Ang II, while ARBs directly block the binding of Ang II to angiotensin II type 1 receptors [8]. These mechanisms help relax blood vessels and reduce pressure on kidneys. Additionally, ACEIs may offer additional cardiovascular protection by increasing bradykinin levels and promoting the production of Ang-(1–7), which counteracts Ang II's vasoconstrictive effects [9].

The comparative effectiveness of ACEIs vs. ARBs in preventing major cardiovascular events (MACEs) in patients with diabetes, particularly older adults, remains uncertain. Meta-analyses of randomized controlled trials (RCTs) suggest ACEIs reduce all-cause mortality, cardiovascular mortality, and major cardiovascular events (MACEs) for patients with diabetes, whereas ARBs demonstrated no benefits [10, 11]. However, a head-to-head RCT found no significant difference between ACEIs and ARBs on MACEs (ARBs vs. ACEIs relative risk [RR] 1.01, 95% CI 0.94–1.09) [12]. Most observational studies have showed neutral findings regarding the comparative risk of MACEs between ACEIs and ARBs [13–18]. Nevertheless, these studies were limited by prevalent user bias, selection bias, and the underrepresentation of older patients (age ≥ 65 years) with T2DM (Table S1).

To address this gap, we directly compare the effects of ACEIs and ARBs on MACEs in older patients with T2DM through a target trial emulation approach [19]. Our goal was to answer the causal question that has not been previously answered, "What would have happened if older patients with T2DM initiated ACEI had, contrary to fact, instead initiated the ARB?".

Methods

Data source

This study utilized data from the Yinzhou Regional Health Care Database (YRHCD) [20], which covers 99% of Yinzhou (the largest district of Ningbo city in eastern China) District's 2.53 million residents by 2021. Established in 2006 by the Yinzhou District Centre for Disease Control and Prevention, the YRHCD integrates personal

data from population census, primary care, outpatient and inpatient electronic medical records, routine health check information, and death reports. These data sources are inherently linked using unique identifiers, ensuring minimal or no loss to follow-up. Electronic health records (EHRs) in the YRHCD were collected from a regionally representative network of healthcare services, comprising 5 general hospitals, 24 township health centers, and 265 community health service stations. The EHRs include: (a) diagnoses data including the name, type, code (International Classification of Diseases, Tenth Revision [ICD-10]), and date of a diagnosis; (b) prescription data including brand and generic names, Anatomical Therapeutic Chemical Classification of Medications (ATC) code, prescription date, filled amount, medication specification, and usage regimen in free text. Additionally, the database includes all death certificates issued within the district, regardless of whether deaths occurred in or outside of hospital, as recorded in the death reporting system.

Target trial specification and emulation

Using the target trial emulation framework [19], we specified the protocol of a target trial that compares the effects of ACEIs vs. ARBs on MACEs among older patients with T2DM (Table S2) This study followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines for observational research [21].

Study population and design

An active-comparator new-user (ACNU) design was employed to control confounding by indication and prevalent user bias [22]. Patients aged ≥ 65 years with T2DM (ICD-10 code: E11) who were new users of ACEIs or ARBs between January 1, 2010 to May 31, 2023 were included. New users were those filling their first prescription of ACEIs or ARBs during the study period, without prior use in the preceding year (1 year washout period). The cohort entry date (T_0) was the date of the first prescription. Exclusion criteria included missing data on age or sex, history of hospitalization for myocardial infarction (MI) or stroke, and simultaneous use of ACEIs and ARBs at T_0. The longitudinal study design is illustrated in Figure S1.

Treatment strategies

We compared two treatment strategies: initiation and continued use of long-acting ACEIs (including enalapril, lisinopril, perindopril, benazepril, fosinopril, imidapril, and ramipril) vs. initiation and continued use of ARBs (including losartan, valsartan, irbesartan, candesartan, telmisartan, olmesartan, and azilsartan). For ACEIs, captopril was excluded due to its rapid absorption and short half-life, and its use in hypertensive emergencies rather than long-term management [23–26]. ATC codes of these drugs were detailed in Table S3.

Covariates

Potential confounders were identified through a literature review and integrated into a directed acyclic graph (DAG) to guide the modeling strategy (Figure S2) [27–29]. Based on the DAG, the following 48 baseline covariates were extracted, including demographics (e.g., age, sex), vital signs (e.g., systolic blood pressure [SBP], diastolic blood pressure [DBP], body mass index [BMI]), laboratory measurements (e.g. hemoglobin A1c [HbA1c], estimated glomerular filtration rate [eGFR] and potassium level), diabetes severity, cardiovascular and other comorbidities (e.g. chronic obstructive pulmonary disease, liver disease), comedications (e.g., aldosterone antagonist, calcium channel blocker [CCB], beta blocker), and healthcare utilizations (e.g., number of inpatient, outpatient and primary care visits). Except demographics, all other covariates were also updated at each month during the follow-up for informative censoring adjustment. Detailed definitions and look-back windows for covariates are provided in Table S4.

Outcomes

The primary outcome was 3-point MACE, including hospitalized MI, hospitalized stroke, and all-cause mortality. Since YRHCD lacks accurate data on cause-specific death, all-cause mortality was used as a proxy, given cardiovascular deaths constitute over 40% of deaths among patients with diabetes [30]. Death was confirmed through the death reporting system. Secondary outcomes included 4-point MACE, i.e., adding hospitalized heart failure (HF) to 3-point MACE, and the individual components of 4-point MACE except hospitalized MI due to small number of events (62 total, 6 ACEIs initiators, 56 ARBs initiators). Cardiovascular events were defined by ICD-10 codes of the primary hospital diagnosis (Table S5).

Follow-up

Patients were followed from T_0 to the occurrence of study outcome, or the administrative end of follow-up (May 31, 2024), whichever came first. As the per-protocol effect was our main causal estimand of interest, patients were censored upon initial ACEIs or ARBs treatment deviation (Table S6), defined as treatment discontinuation, augmentation (adding ACEIs to ARBs or vice versa), or switching between ACEIs to ARBs. Discontinuation of ACEIs or ARBs treatment was defined as the absence of a new prescription for the same drug within 90 days (a grace period to allow for some delay in refills) of the last day of the previous prescription. Days' supply frequency

of prescriptions was listed in Table S7. To account for the information of monthly updated covariates during follow-up, the analytic dataset was set up in the format of a counting process where each row represents a person-month.

Statistical analysis

The inverse probability of treatment weight (IPTW) was used to adjust for confounding by indication [31]. By using logistic regression, we estimated propensity scores (PS), the probability of receiving ACEIs initiation vs. ARBs initiation conditional on all baseline covariates included in the minimal adjustment set, as determined by the DAG presented in Figure S2. Patients initiating ACEIs were weighted by 1/PS, and those initiating ARBs by 1/(1-PS), with weights stabilized by adding the marginal probability of ACEIs initiation vs. ARBs initiation to the numerator. Standardized mean differences (SMDs) were calculated to evaluate covariates balance before and after weighting, with a SMD of > 0.1 indicating meaningful imbalance.

Furthermore, inverse probability of censoring weight (IPCW) was applied to address the selection bias from informative censoring due to treatment deviation. At each follow-up month i, adherence probability to the initial treatment was estimated by pooled logistic regression, based on initial treatment and all baseline and monthly updated covariates. IPCWs were calculated as the inverse of cumulative probability of adherence from T_0, stabilized by the cumulative probability of adherence conditional on only initial treatment [32]. For example, the stabilized IPCW at follow-up month k was calculated as: $IPCW^{stab}(k) = \prod_{i=1}^{k} \frac{\Pr(C_i=0|\bar{C}_{i-1}=0, A)}{\Pr(C_i=0|\bar{C}_{i-1}=0, A, \bar{\boldsymbol{L}}_i)}$, where C indicates treatment deviation, A represents the initial treatment, and $\bar{\boldsymbol{L}}_i$ denotes the history of baseline covariates included in the minimal adjustment set and all monthly updated covariates from T_0 to month i. The numerator represents the probability of remaining uncensored given only prior treatment adherence and initial treatment, while the denominator further conditions on history of all covariates. These weights account for the potential selection bias induced by informative censoring of treatment deviations, ensuring that comparisons between treatment groups remain unbiased. IPCW weights are then incorporated into the estimation procedure to approximate the counterfactual treatment effects under full adherence [33].

To estimate the per-protocol effects of treatment strategies, marginal structural models (MSMs) were fitted by pooled logistic regression, incorporating treatment strategy, month (and its squared term) as predictors, and weighted by the product of IPTW and IPCW [32]. Weights were truncated at the 0.1th and 99.9th percentile to reduce the impact of extreme values before fitting the MSM. Adjusted hazard ratios (aHRs) were derived, and cumulative incidence curves were generated to compare outcome incidences and calculate 1-year absolute risks and risk difference. Confidence intervals (CIs) were estimated using non-parametric bootstrapping with 500 samples. Two-tailed P values were calculated via non-parametric bootstrap tests, with a statistical significance level of 0.05. Details of the weights are in Table S8.

Missing rates of SBP, DBP, BMI, HbA1c, eGFR, and potassium were 24.1%, 24.1%, 44.4%, 92.9%, 81.0% and 90.8% at baseline and 13.6%, 13.6%, 27.3%, 88.2%, 73.7% and 84.3% during follow-up, respectively. Missing values of SBP and DBP (missing rate < 30%) were imputed using the multiple imputation by chained equation with classification and regression trees [34], with the imputation model including treatment, outcome, all covariates (except vital signs), and the Nelson-Aalen estimator of the cumulative hazard function. 5 imputed datasets were generated, and the IPTW, IPCW and effect estimates were estimated separately in each imputed data set and then pooled using Rubin's rule [35].

Subgroup and sensitivity analyses

We examined the potential effect modification across the following subgroups: (1) age (> 75 vs. ≤ 75 years), (2) sex (male vs. female), (3) major atherosclerotic CVD (arterial disease, other ischemic heart disease [except MI], other cerebrovascular disease [except stroke], and peripheral vascular disease), (4) HF, (5) use of other antihypertensive therapy (i.e., calcium channel blockers, beta-blockers, loop diuretics, and other diuretics), (6) insulin therapy, and (7) calendar year (2010–2018 vs. 2019–2021), detailed definitions of subgroup variables were shown in Table S4. IPTWs and IPCWs were re-estimated for each subgroup, and weighted MSMs were refitted to estimate per-protocol effects [36]. P values for interaction were calculated through inverting the corresponding bootstrapped confidence interval of the difference of HRs between these two subgroups [37].

We performed following sensitivity analyses to assess the robustness of our results. First, to account for potential carry-over effect, we extended follow-up to 30, 60, and 90 days (latency period) after discontinuation of ACEIs or ARBs. Second, to mitigate the potential misclassification of treatment discontinuation due to the grace period definition, we varied it from 90 days to 0, 30 and 60 days. Third, to eliminate the influence of different follow-up durations between two treatment groups, intention-to-treat (ITT) analysis with maximum follow-up period of 6 and 12 months were performed, respectively. Fourth, to eliminate the potential influence of ACEIs and ARBs use before the washout period on study

results, we reperformed our analyses by redefining new users of ACEIs and ARBs as patients without any prior use of ACEIs and ARBs. Last, to address the adherence-related bias, we (1) analyzed baseline covariates among ACEIs initiators with 1, 2, 3, and ≥4 prescriptions; (2) identified cough diagnoses and cough suppressant use within 3 months before and 1 month after treatment deviation; (3) excluded patients with cough diagnoses or cough suppressant use during the 1-year baseline period, to minimize the effect of cough recurrence on prescribing ACEIs and its adherence; (4) required patients to have ≥2 prescriptions, with follow-up beginning from the second prescription, to increase the probability the patients actually took the medication; (5) combined exclusion criteria from (3) and (4) to further refine the cohort and reduce adherence-related biases.

All analyses were performed using R 4.1.2 software (The R Project for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

The study included 18,558 older patients with T2DM who initiated ACEIs (n = 1,641) or ARBs (n = 16,917) between January 1, 2010, and May 31, 2023 (Figure S3). ACEIs initiators primarily used enalapril (39.4%), benazepril (25.9%), and perindopril (24.7%), while ARBs initiators commonly used telmisartan (26.7%), irbesartan (26.0%), and valsartan (23.9%). Baseline characteristics were well-balanced after weighting (Table 1, Figure S4). Follow-up exceeded 120 days for 1070 (65.2%) ACEIs initiators and 14,737 (87.1%) ARBs initiators (Table S6).

ACEIs and ARBs initiators were of the similar age (72 years), SBP (129.81 mmHg vs. 129.82 mmHg), DBP (78.00 mmHg vs. 78.27 mmHg) and BMI (23.81 Kg/m^2 vs. 23.93 Kg/m^2). ACEIs initiators included more males (50.7% vs. 44.6%) and milder diabetes severity, with lower rates of diabetes-related complications such as retinopathy (4.9% vs. 5.6%), nephropathy (2.4% vs. 3.1%), and neuropathy (1.5% vs. 2.2%). Cardiovascular comorbidities were higher among ACEIs initiators, including arterial disease (8.3% vs. 7.1%), other ischemic heart disease (except MI) (23.4% vs. 18.7%), and other cerebrovascular disease (except stroke) (12.8% vs. 12.3%), which corresponded to greater use of cardiovascular medications, such as beta blockers (21.5% vs. 16.6%), diuretic (16.6% vs. 13%), platelet inhibitors (27.3% vs. 21.8%) and statins (28.6% vs. 24.9%). Both groups had similar outpatient and primary care visits (30 vs. 31 visits/year).

Comparative effectiveness of aceis and ARBs

For the 3-point MACE, during a median follow-up of 1.36 (interquartile range [IQR] 0.66–2.83) years, 85 events occurred among 1,641 ACEIs initiators (median follow-up of 0.54 [IQR 0.30–1.35] years) and 1,730 among 16,917 ARBs initiators (median follow-up of 1.45 [IQR, 0.74–2.95] years), respectively. Incidence rates were 44.0 (95% CI 35.5–54.3) and 47.2 (95% CI 45.2–49.5) per 1000 person-years, respectively (Table 2). The aHR was 0.86 (95% CI 0.68–1.10, p = 0.229), indicating a slightly lower risk of 3-point MACE among ACEIs initiators (Table 2). Weighted cumulative incidence curves showed 1-year absolute risk of 4.61% (95% CI 3.15-6.08%) for ACEIs compared to 4.91% (95% CI 4.56–5.26%) for ARBs, with a 1-year absolute risk difference of – 0.30% (95% CI – 1.80–1.21%) (Fig. 1 Panel A).

For the 4-point MACE outcome, during a median follow-up of 1.30 (IQR, 0.58–2.67) years, the aHR for ACEIs versus ARBs was 0.83 (95% CI 0.69–0.99, p = 0.044) (Table 2), with weighted cumulative incidence curves showing an early divergence in absolute risks of 4-point MACE favoring ACEIs (Fig. 1 Panel B).

For other secondary outcomes, the aHRs for hospitalized HF, hospitalized stroke and all-cause mortality were 0.86 (95% CI 0.67–1.11, p = 0.245), 0.80 (95% CI 0.62–1.03, p = 0.081), and 0.87 (95% CI 0.47–1.60, p = 0.653), respectively. These findings further support the cardiovascular benefits for short-term use of ACEIs (Table 2, Figure S5 Panels A-C).

Subgroup and sensitivity analyses

The lower risks of 3-point and 4-point MACE for ACEIs were consistent across all subgroups, with no significant interactions observed (Figure S6, Figure S7).

Overall, sensitivity analyses aligned with the primary findings (Fig. 2). When latency periods of 30, 60, and 90 days were considered, the aHRs for 4-point MACE consistently showed advantages of ACEIs (Table S9). Across grace periods of 0, 30, and 60 days, ACEIs initiators consistently showed lower MACE risks than ARBs initiators (Table S10). For ITT analysis with maximum follow-up of 6 months, the aHRs were 0.74 (95% CI 0.52–1.06) for 3-point MACE and 0.77 (95% CI 0.61–0.98) for 4-point MACE. Extending the maximum follow-up to 12 months yielded consistent results (Table S11). When new users were redefined as patients without any prior use of ACEIs and ARBs, 1,605 ACEIs initiators and 16,508 ARBs initiators were included (Table S12). ACEIs initiators still showed lower MACE risks than ARBs initiators (Table S13). As shown in Table S14, compared to those with 2, 3, or ≥4 prescriptions, ACEIs initiators with only 1 prescription filled often had a higher baseline prevalence of cardiovascular comorbidities, including congestive heart failure (9.4% vs. 8.1%, 2.9% and 3.0%), atrial fibrillation (4.3% vs. 2.6%, 2.9% and 1.8%), and arrhythmia disorder (9.0% vs. 9.9%, 5.1% and 5.2%). They also had a higher baseline medication rates of aldosterone antagonists (9.0% vs. 4.8%, 2.2% and 2.8%), loop diuretic (8.7%

Table 1 Baseline characteristics of patients before and after weighting

Covariates	Unweighted cohort			Weighted cohort		
	ACEIs *N* = 1641	ARBs *N* = 16,917	SMD	ACEIs *N* = 1643	ARBs *N* = 16,917	SMD
Demographics						
Age (median, IQR), years	72 (68, 78)	72 (68, 78)	0.002	72 (68, 78)	72 (68, 78)	0.007
Sex, Males	832 (50.7)	7542 (44.6)	0.123	740 (45.1)	7634 (45.1)	0.001
Vital signs[a]						
SBP (median, IQR), mmHg	129.81 (126.09, 134.24)	129.82 (126.00, 134.00)	0.001	129.71 (125.71, 134.86)	129.84 (125.64, 134.56)	0.007
DBP (median, IQR), mmHg	78.00 (75.12, 80.94)	78.27 (75.55, 80.86)	0.035	78.00 (74.67, 81.52)	78.25 (75.00, 81.38)	0.009
BMI (median, IQR), Kg/m^2	23.81 (22.14, 25.82)	23.93 (22.23, 25.83)	0.037	–	–	–
Laboratory tests[b]						
HbA1c (median, IQR), %	6.90 (6.03, 8.10)	6.80 (6.10, 8.00)	0.143	–	–	–
eGFR (median, IQR), mL/min/1.73 m^2	91.23 (76.77, 97.54)	91.69 (77.43, 97.24)	0.018	–	–	–
Potassium (median, IQR), mmol/L	4.20 (4.00, 4.73)	4.10 (4.00, 4.57)	0.048	–	–	–
Indications of diabetes severity						
Diabetes retinopathy	81 (4.9)	947 (5.6)	0.030	89 (5.4)	937 (5.5)	0.005
Diabetes nephropathy	40 (2.4)	528 (3.1)	0.042	56 (3.4)	518 (3.1)	0.018
Diabetes neuropathy	24 (1.5)	371 (2.2)	0.055	38 (2.3)	360 (2.1)	0.011
Diabetes circulatory complication	12 (0.7)	149 (0.9)	0.017	13 (0.8)	147 (0.9)	0.006
Hypoglycemia	14 (0.9)	186 (1.1)	0.025	16 (0.9)	182 (1.1)	0.013
Cardiovascular comorbidities						
Arterial disease	136 (8.3)	1195 (7.1)	0.046	123 (7.5)	1214 (7.2)	0.013
Ischemic heart disease	384 (23.4)	3158 (18.7)	0.116	308 (18.8)	3228 (19.1)	0.008
Cerebrovascular disease	210 (12.8)	2080 (12.3)	0.015	204 (12.4)	2088 (12.3)	0.002
Congestive heart failure	81 (4.9)	523 (3.1)	0.094	55 (3.4)	551 (3.3)	0.005
Peripheral vascular disease	120 (7.3)	1063 (6.3)	0.041	110 (6.7)	1079 (6.4)	0.013
Atrial fibrillation	40 (2.4)	250 (1.5)	0.069	23 (1.4)	264 (1.6)	0.014
Arrhythmia disorder	109 (6.6)	911 (5.4)	0.053	87 (5.3)	930 (5.5)	0.010
Hypertension	1539 (93.8)	16,245 (96.0)	0.102	1578 (96.0)	16,213 (95.8)	0.010
Valvular disease	1 (0.1)	6 (0.0)	0.012	0 (0.0)	6 (0.0)	0.011
Other comorbidities						
COPD	313 (19.1)	2942 (17.4)	0.044	288 (17.5)	2967 (17.5)	< 0.001
Liver disease	62 (3.8)	644 (3.8)	0.001	62 (3.8)	644 (3.8)	< 0.001
Renal disease	100 (6.1)	1155 (6.8)	0.030	121 (7.4)	1145 (6.8)	0.024
Obesity	2 (0.1)	16 (0.1)	0.008	2 (0.1)	16 (0.1)	< 0.001
Cancer	44 (2.7)	386 (2.3)	0.026	42 (2.6)	393 (2.3)	0.015
Comedications for diabetes						
Insulin	170 (10.4)	1756 (10.4)	0.001	176 (10.7)	1757 (10.4)	0.011
Sulfonylurea	622 (37.9)	6551 (38.7)	0.017	643 (39.1)	6538 (38.7)	0.010
SGLT2i	27 (1.6)	227 (1.3)	0.025	23 (1.4)	232 (1.4)	0.005
DPP-4i	56 (3.4)	536 (3.2)	0.014	54 (3.3)	540 (3.2)	0.006
Thiazolidinedione	89 (5.4)	1017 (6.0)	0.025	97 (5.9)	1008 (6.0)	0.003
Glinide	135 (8.2)	1485 (8.8)	0.020	144 (8.8)	1477 (8.7)	0.001
Metformin	552 (33.6)	5654 (33.4)	0.005	561 (34.1)	5658 (33.4)	0.015
Alpha-glucosidase inhibitor	377 (23.0)	3865 (22.8)	0.003	380 (23.1)	3867 (22.9)	0.006
Other comedications						
Aldosterone antagonists	68 (4.1)	471 (2.8)	0.074	50 (3.0)	492 (2.9)	0.006
CCB	753 (45.9)	8235 (48.7)	0.056	806 (49.0)	8195 (48.4)	0.012
BB	353 (21.5)	2805 (16.6)	0.126	273 (16.6)	2877 (17.0)	0.010
Loop diuretic	60 (3.7)	440 (2.6)	0.061	49 (3.0)	457 (2.7)	0.017
Other diuretic	211 (12.9)	1762 (10.4)	0.076	178 (10.8)	1799 (10.6)	0.006

Table 1 (continued)

Covariates	Unweighted cohort			Weighted cohort		
	ACEIs *N* = 1641	ARBs *N* = 16,917	SMD	ACEIs *N* = 1643	ARBs *N* = 16,917	SMD
Thiazide	396 (24.1)	5095 (30.1)	0.135	485 (29.5)	5006 (29.6)	0.002
Platelet inhibitor	448 (27.3)	3689 (21.8)	0.128	372 (22.7)	3771 (22.3)	0.009
Anticoagulant	13 (0.8)	67 (0.4)	0.052	6 (0.4)	73 (0.4)	0.006
PPI	336 (20.5)	3522 (20.8)	0.008	341 (20.7)	3517 (20.8)	0.001
NSAID	343 (20.9)	3312 (19.6)	0.033	326 (19.8)	3332 (19.7)	0.003
Statin	469 (28.6)	4210 (24.9)	0.084	409 (24.9)	4264 (25.2)	0.006
Healthcare utilizations						
N of inpatient visits (median, IQR)	0 (0, 0)	0 (0, 0)	0.014	0 (0, 0)	0 (0, 0)	0.013
N of outpatient and primary care visits (median, IQR)	30 (10, 65)	31 (11, 70)	0.056	31 (10, 68)	31 (11, 70)	0.001

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; BB, beta blocker; BMI, body mass index; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; DPP-4i, dipeptidyl peptidase 4 inhibitors; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; IQR, interquartile range; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; PPI, proton pump inhibitor; SBP, systolic blood pressure; SGLT2i, sodium-glucose transport protein 2 inhibitors; SMD, standardized mean differences.

[a]Proportion of missing variables: 24.1% for SBP, 24.1% for DBP, and 44.4% for BMI. Covariates with a low missing rate (< 30%, SBP and DBP) were imputed using multiple imputations, and the imputation models included the indicator of initial treatment, all covariates (except vital signs), the event indicator for the outcome, and the Nelson-Aalen estimate of the baseline and each month's cumulative hazard. Covariate with a high missing rate (≥ 30%, BMI) was excluded from the propensity scores calculation.

[b]Proportion of missing variables: 92.9% for HbA1c, 81.0% for eGFR, and 90.8% for potassium. Due to the high missing rates (≥ 30%), all laboratory measurements were excluded from the propensity scores calculation.

Table 2 Crude and adjusted HRs for outcomes among aceis initiators and ARBs initiators

Treatment	Follow-Up (Years), Median (IQR)	*N*	Events	Person-years	Incidence rate (per 1000 person-years) (95% CI)	Crude HR (95% CI)	Adjusted HR[a] (95% CI)
Primary outcome							
3-point MACE							
ACEIs	0.54 (0.30, 1.35)	1641	85	1933	44.0 (35.5, 54.3)	0.89 (0.71, 1.10)	0.86 (0.68, 1.10)
ARBs	1.45 (0.74, 2.96)	16,917	1730	36,580	47.2 (45.2, 49.5)	Reference	Reference
Secondary outcome							
4-point MACE							
ACEIs	0.50 (0.29, 1.30)	1641	158	1855	85.2 (73.1, 99.0)	0.97 (0.83, 1.14)	0.83 (0.69, 0.99)
ARBs	1.37 (0.67, 2.79)	16,917	2797	34,691	80.6 (77.8, 83.6)	Reference	Reference
Hospitalized HF							
ACEIs	0.51 (0.29, 1.32)	1641	85	1918	44.3 (35.8, 54.8)	1.07 (0.86, 1.33)	0.86 (0.67, 1.11)
ARBs	1.45 (0.74, 3.02)	16,917	1373	37,122	37.0 (35.1, 39.0)	Reference	Reference
Hospitalized stroke							
ACEIs	0.54 (0.30, 1.35)	1641	71	1936	36.7 (28.9, 46.3)	0.83 (0.65, 1.06)	0.80 (0.62, 1.03)
ARBs	1.45 (0.74, 2.96)	16,917	1548	36,666	42.2 (40.2, 44.3)	Reference	Reference
All-cause mortality							
ACEIs	0.57 (0.30, 1.42)	1641	13	2001	6.50 (3.62, 11.40)	0.82 (0.47, 1.44)	0.87 (0.47, 1.60)
ARBs	1.54 (0.80, 3.22)	16,917	287	39,163	7.33 (6.52, 8.24)	Reference	Reference

ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CI confidence interval; HF, heart failure; HR, hazard ratio; IQR, interquartile range; MACE, major adverse cardiac event.

[a]Adjusting for demographics, vital signs (except BMI), comorbidities, comedications, healthcare utilizations, and censorship.

vs. 4.4%, 2.2% and 2.2%), and other diuretic (19.9% vs. 16.5%, 12.5% and 9.8%). ACEIs initiators had a slightly higher frequency for cough diagnosis (7.8% vs. 5.5%) and cough suppressants use (17.7% vs. 15.4%) within 3 months before or 1 month after treatment deviation, with occurred earlier compared to ARBs initiators (median time from T_0: 0.4 years vs. 1.3 years) (Table S15). Excluding patients with cough diagnoses or cough suppressant

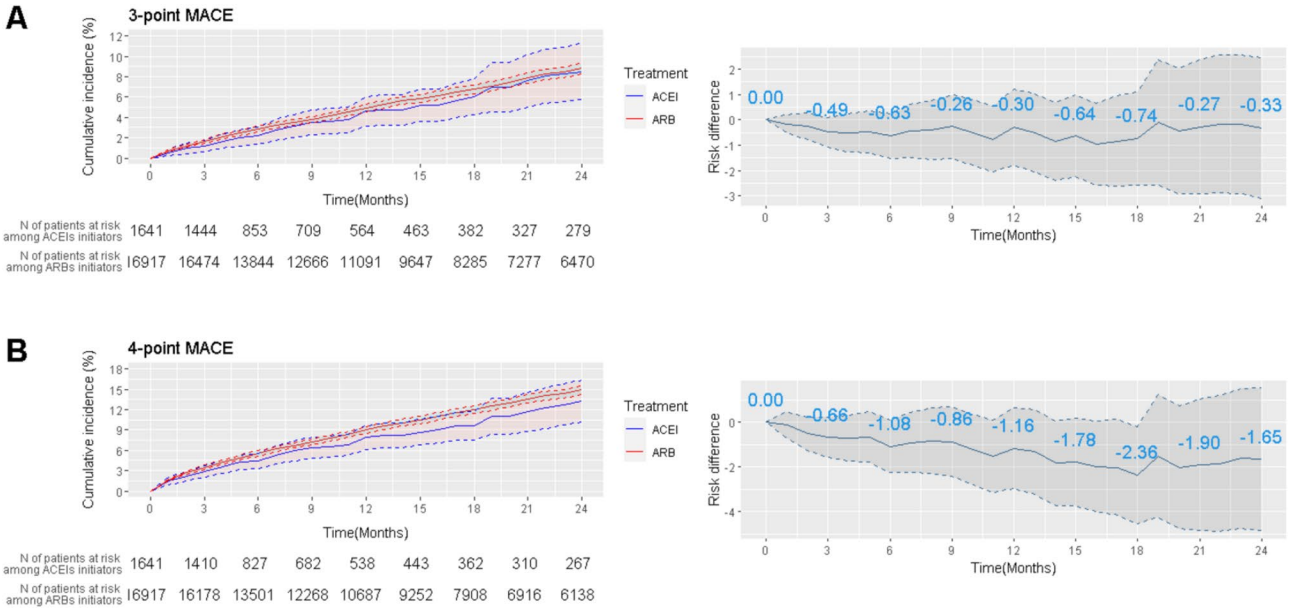

Fig. 1 Weighted cumulative incidence curves and risk difference for **A** 3-point MACE and **B** 4-point MACE. ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CI, confidence interval; MACE, major adverse cardiac event

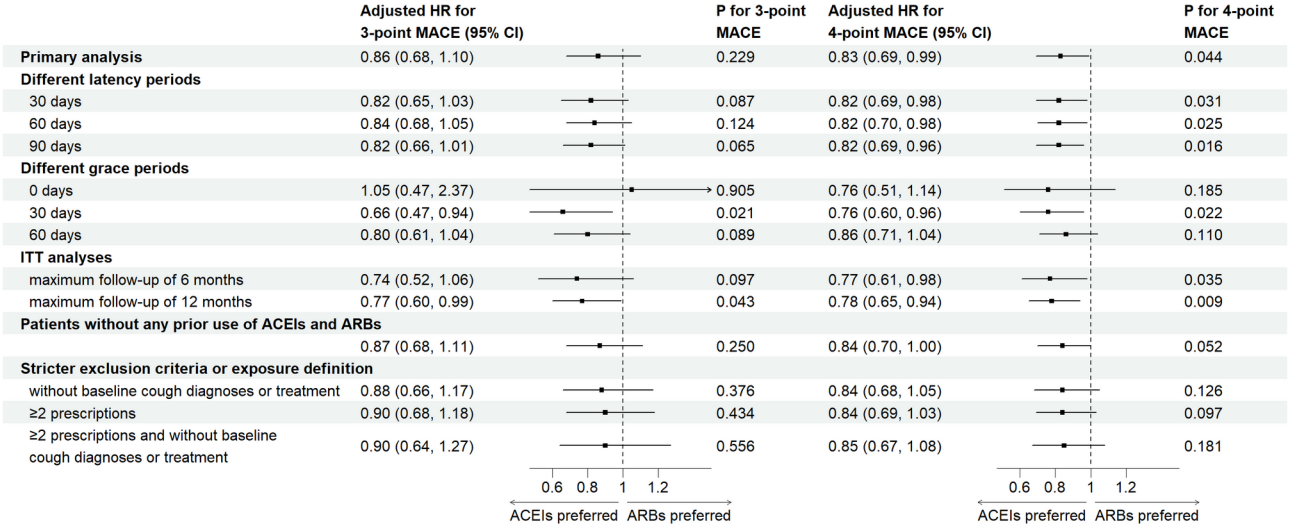

Fig. 2 Adjusted HRs[a] of sensitivity analyses. ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; MACE, major adverse cardiac event. [a]Adjusting for demographics, vital signs (except BMI), comorbidities, comedications, healthcare utilizations, and censorship

use at baseline resulted in consistent findings with primary analysis but extended ACEIs follow-up (ACEIs vs. ARBs: 0.65 years vs. 1.50 years, aHR 0.88 [95% CI 0.66–1.17] for 3-point MACE; 0.60 years vs. 1.41 years, aHR 0.84 [95% CI 0.68–1.05] for 4-point MACE, Table S16). Among the 1364 ACEIs initiators and 15,747 ARBs initiators with ≥ 2 prescriptions, the findings remained similar, with extended ACEIs follow-up (0.69 years vs. 1.40 years, aHR 0.90 [95% CI 0.68–1.18] for 3-point MACE; 0.66 years vs. 1.33 years, aHR 0.84 [95% CI 0.69–1.03] for 4-point MACE, Table S16). And similar results were observed in patients with ≥ 2 prescriptions and without baseline cough diagnoses or cough suppressant use, with ACEIs and ARBs initiators having longer follow-up (0.85 years vs. 1.61 years, aHR 0.90 (95% CI 0.64–1.27) for 3-point MACE; 0.84 years vs. 1.53 years, aHR 0.85 (95% CI 0.67–1.08) for 4-point MACE).

Discussion

In the cohort study of 18,558 older patients with T2DM, ACEIs initiation was associated with a trend toward lower MACE risk compared with ARBs in short-term

use. The results were consistent across subgroups and sensitivity analyses, underscoring the potential preference for ACEIs over ARBs in managing cardiovascular risk in this population. To the best of our knowledge, this is the first study to directly compare CVD risks between ACEIs and ARBs in older patients with T2DM specifically using the target trial emulation framework, providing novel insights into the comparative effectiveness.

Our findings align with a prior systematic review and meta-analysis of RCTs showing ACEIs, but not ARBs, reduce MACE risk compared to placebo [10, 11]. The PROGRESS and HOPE trials, which both included patients around 65 years old and followed them more than 3 years, reported significant MACE reductions with ACEIs compared to placebo (RR 0.74, 95% CI 0.66–0.84 and 0.78, 95% CI 0.70–0.86, separately) [38, 39], whereas the PROFESS trial with a mean follow-up of 2.5 years and an average participant age of 66 years and TRANSCEND trial with a median follow-up of 4.7 years and an average participant age of 67 years found less pronounced reduction in MACE with ARBs compared to placebo (HR 0.94, 95% CI 0.87–1.01 and 0.92, 95% CI 0.81–1.05, respectively) [40, 41]. Among patients with T2DM, the ADVANCE trial which included 11,140 individuals with an average age of 66 years, indicated that ACEIs reduced MACE and major microvascular events compared to placebo during a mean 4.3-year follow-up, with consistent results among older patients (RR 0.89, 95% CI 0.79–1.00) [42]. Conversely, the ROADMAP trial found no MACE reduction with ARBs compared to placebo (HR 1.00, 95% CI 0.75–1.33) during a median follow-up of 3.2 years among 4,447 patients with an average of 58 years [43]. Although the ONTARGET trial, a head-to-head comparison ramipril and telmisartan, provided strong evidence for no difference in MACE risk (ARBs vs. ACEIs RR 1.01, 95% CI 0.94–1.09) during a median follow-up of 4.7 years among 25,620 patients with an average age of 66.5 years [12], emulation analyses suggested a slight advantage for telmisartan (ARBs vs. ACEIs HR, 0.96, 95% CI 0.95–0.98) [44]. However, these studies were not specific to T2DM (37.5% and 60.0% of participants in the target and emulated trial, respectively) or Asian patients. Notably, the average age of patients in our study was 73.5 years, higher than in prior trials, indicating a greater cardiovascular risk profile, which could result in earlier detection of treatment benefits.

However, previous observational studies have generally not demonstrated a clear cardiovascular advantage of ACEIs over ARBs among patients with diabetes [13–18], which aligns with the neutral findings observed in the LEGEND-HTN study [45]. The LEGEND-HTN study, a comprehensive and large-scale observational analysis of five first-line antihypertensive drug classes, has found no significant differences on the comparative effectiveness of ACEIs and ARBs in a general hypertensive population [45]. However, as shown in Table S17, our study incorporates several key study design differences compared to LEGEND-HTN study that contribute to the novelty of our findings. Firstly, our study adopted the target trial emulation framework explicitly to promote valid causal inference, and adjusted baseline confounding and selection bias caused by informative censoring during the follow-up simultaneously by IPTW-IPCW weighted MSM, which both enhanced the credibility of our results in real-world settings. Secondly, our study focused on older patients with T2DM, which was underrepresented in the LEGEND-HTN study (≤ 40% of patients aged 65 or older, Table S18). Compared to general hypertensive population, older patients with T2DM exhibited an elevated cardiovascular risk, potentially explaining the greater cardiovascular benefit observed with ACEIs compared to ARBs in our study. This suggests ACEIs may offer more pronounced benefits in higher-risk individuals, particularly for stroke outcome [15, 16]. Furthermore, earlier studies often include captopril, which may be used in hypertensive emergencies thus induce confounding by indication, potentially biased results toward the null [24–26, 46]. By excluding captopril, our study allowed a clearer comparison of long-acting ACEIs and ARBs.

Notably, Wu et al. (ACEIs vs. ARBs HR 1.12, 95% CI 1.02–1.24) and Pai et al. (ARBs vs. ACEIs HR 0.75, 95% CI 0.61–0.91) reported that ARBs were superior to ACEIs for stroke risk among adults with diabetes and hypertension [15, 16]. Wu et al.'s study introduced potential selection bias by requiring cover rate ≥ 70% and lacked clarity on censoring criteria, making it unclear whether an ITT or per-protocol approach was used [15]. Similarly, Pai et al.'s study evaluated some associations rather than causal effects of treatment, treating prescription changes as a time-dependent variable [16]. In contrast, our robust target trial emulation framework enables more accurate treatment effect assessment, supporting the cardiovascular benefits of ACEIs.

The study enrolled substantially fewer ACEIs initiators compared to ARBs initiators, with the former also exhibiting a shorter follow-up period. This disparity aligns with previous studies demonstrating that ACEIs use is associated with an increased risk of cough [47], a side effect particularly pronounced in East Asian populations (RR 2.7, 95% CI 1.6–4.5 compared with white populations) [48]. In the absence of a specific preference on CVD risk management outlined in the Chinese clinical guideline [7], physicians would prefer ARBs in clinical practice to minimize the safety concerns related to adverse effects [49], potentially leading to a short follow-up. Additionally, the current and previous Chinese guideline for management of older adults with diabetes [7, 50] recommended ARB or CCB over other antihypertensive

drugs, citing their lower risk of orthostatic hypotension based on prior evidence [51, 52]. This guidance further reinforces the preference for ARBs in clinical practice. During follow-up, ACEIs users experiencing coughing or similar symptoms may have attributed these side effects to their medication, prompting treatment discontinuation or switching. Notably, as many Chinese cough suppressants are over-the-counter [53] and dietary remedies are commonly used to address cough symptoms [54], our analysis do not fully capture all patients with cough symptoms. Furthermore, ACEIs initiators, particularly those with fewer prescriptions, exhibited a higher prevalence of cardiovascular comorbidities and were more likely to receive diuretic medications—both factors previously associated with non-adherence to antihypertensive therapy [55, 56]. These characteristics may have contributed to the lower adherence rates observed among ACEIs users in our cohort, and we acknowledge that additional factors—particularly socioeconomic status—could also influence the adherence pattern of ACEIs users [57].

Clinical treatment decisions should always be based on weighing the effectiveness against the safety profile (on the absolute scale) [58]. In different clinical practice settings, there is substantial regional variation in the prescribing rates of ACEIs and ARBs: ACEIs are more frequently prescribed than ARBs in hypertensive diabetic patients in the United States or Europe [59–61], whereas ARBs are more frequently prescribed than ACEIs in East Asia [62–64]. As aforementioned, the prescribing pattern in Asian population may be driven by concerns about ACEIs-induced cough. Together with the biological mechanisms [9] and the RCT evidence outlined above suggesting enhanced cardiovascular protection with ACEIs compared with ARBs [38–43], our study provides real-world evidence that ARBs may not be preferred over ACEIs in Chinese clinical practice, especially for older patients with T2DM at higher CVD risk. For these patients, given that the impact of ACEIs-induced cough is relatively minor compared to the cardiovascular benefits, clinicians should not avoid prescribing ACEIs based on the potential discomfort caused by cough. Instead, they should carefully evaluate the net clinical benefit, considering the individual patient's health status and preference.

Key strengths of this study include the use of target trial emulation, which provides a framework to promote valid causal inference, the use of an ACNU design, which minimizes time-related biases and indication bias, and comprehensive adjustment for confounders by IPTW, which ensures baseline comparability between ACEI initiators and ARBs initiators. The application of IPCW addressed potential biases related to treatment deviation, leading to a reliable comparison of ACEIs and ARBs across the whole follow-up. Moreover, evaluating both 3-point and 4-point MACE outcomes provided a thorough assessment of cardiovascular risk, and consistent findings across the per-protocol and intention-to-treat analyses strengthen the study's validity. Additionally, to reflect real-world comparative effectiveness of ACEIs and ARBs in China, we performed variety of sensitivity analyses by excluding patients with cough (by diagnoses or suppressant use) or <2 ACEIs or ARBs prescriptions, which further improved the exchangeability of the treatment groups, enhancing the robustness of our treatment effect estimates. Furthermore, to the best of our knowledge, few studies evaluated the comparative effectiveness of ACEIs vs. ARBs among older patients with T2DM, our findings specifically address this gap and provide valuable new evidence, particularly for the Asian population.

Several limitations warrant consideration. Firstly, inherent limitations of the YRHCD affect the internal validity of our findings. Specifically, laboratory data quality was suboptimal due to unprocessed raw records and inconsistent documentation, resulting in extensive missingness of baseline laboratory measurements (e.g., $\geq$ 90% missing for HbA1c and potassium, $>80\%$ missing for eGFR, and complete absence of albuminuria and uric acid). Similar to BMI, the pervasive missingness precluded the inclusion of these covariates in IPTW and IPCW adjustments, contributing to residual confounding and limiting our ability to fully address selection bias from informative censoring of treatment deviations. Additionally, cause-of-death data in the YRHCD were recorded as unstructured text rather than standardized coding (e.g., ICD-10), making systematic processing infeasible. Consequently, all-cause mortality was used as a proxy for cardiovascular-specific mortality in our analysis, potentially introducing non-differential misclassification bias due to outcome measurement error. Furthermore, in the YRHCD and other similar EHR-derived databases, cardiovascular outcomes identification primarily relies on ICD-10 codes, which may introduce measurement bias (from coding errors or case underrepresentation), particularly for hospitalized HF. Nevertheless, validation studies have demonstrated using ICD-10 codes to identify cardiovascular outcomes is highly accurate, with positive predictive values (PPVs) exceeding 80% for the majority of hospitalized HF, MI, and stroke cases [65]. Secondly, our data is from a single country, it may limit the generalizability of our findings, though they remain relevant for evaluating relative efficacy within the Chinese older population with T2DM. Furthermore, distinct use patterns of ACEIs and ARBs in Chinese population—influenced by a higher incidence of ACEIs-induced cough and regional guidelines—may constrain the transportability of our results, and caution should be warranted when extrapolating our results to other population. Thirdly, population emigration was not used as a

censoring criterion, though the low out-migration rate from the YRHCD (0.47% during the study period) likely had minimal impact. Additionally, the shorter follow-up period of ACEIs users may have underestimated events in this group. To address this, we performed intention-to-treat analyses and included initiators without baseline cough diagnoses or cough suppressant use and those with at least 2 prescriptions, as well as the combination of the two restrictions. These approaches confirmed the cardiovascular benefits of ACEIs and extended median follow-up duration for ACEIs users in the 3-point MACE outcome from 0.54 years to 0.65, 0.69 and 0.85 years, respectively, with similar increases for 4-point MACE.

Conclusions

This active-comparator, new-user cohort study suggests short-term use of ACEIs is associated with a trend toward lower MACE risk compared to ARBs in older patients with T2DM. Given the level of evidence, healthcare professionals should carefully consider whether ARBs should be preferred over ACEIs for cardiovascular risk management in this population.

Abbreviations

ACEIs	Angiotensin-converting enzyme inhibitors
ACNU	Active-comparator new-user
aHRs	Adjusted hazard ratios
Ang	Angiotensin
ARBs	Angiotensin II receptor blockers
ATC	Anatomical Therapeutic Chemical Classification of Medications
BMI	Body mass index
CCB	Calcium channel blocker
CI	Confidence interval
CVD	Cardiovascular disease
DAG	Directed acyclic graph
DBP	Diastolic blood pressure
EHR	Electronic health record
HF	Heart failure
ICD-10	International Classification of Diseases, Tenth Revision
IPCW	Inverse probability of censoring weight
IPTW	Inverse probability of treatment weight
IQR	Interquartile range
ITT	Intention-to-treat
MACEs	Major cardiovascular events
MI	Myocardial infarction
MSMs	Marginal structural models
RCTs	Randomized controlled trials
RR	Relative risk
PS	Propensity scores
SBP	Systolic blood pressure
SMDs	Standardized mean differences
STROBE	Strengthening the reporting of observational studies in epidemiology
T2DM	Type 2 diabetes mellitus
YRHCD	Yinzhou Regional Health Care Database

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02753-1.

Supplementary Material 1

Acknowledgements

The authors are grateful to John B Buse and Neil R Poulter for their help with the original study protocol.

Author contributions

WZ: data curation, formal analysis, original draft, visualization; TW: conceptualization, methodology, review and editing, supervision; TS: conceptualization, methodology, review and editing, supervision; NH: conceptualization, review and editing; PS: data provision; HL: data provision; XG: project administration; YX: conceptualization, investigation, methodology, review and editing, project administration. All authors read and approved the final manuscript.

Funding

YX is supported by the Young Scientists Fund, National Natural Science Foundation of China (Grant no. 82304245), the Chinese National Key Research R&D Program, Ministry of Science and Technology of China (Grant no. 2021YFC2501300), and the Chinese National Key Research R&D Program, Ministry of Science and Technology of China (Grant no. 2023YFC3604402). TW is supported by the American Diabetes Association (Grant nos. 4-22-PDFPM-06).

Availability of data and materials

The data that support the findings of this study are available from YRHCD but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of YRHCD.

Declarations

Ethics approval and consent to participate

Ethics approval and consent to participate

Consent for publication

The study used only deidentified data and thus was deemed not to require informedconsent.

Competing interests

WZ, TW, NH, PS, HL, XG, YX all have no conflicts of interest that are directly relevant to the content of this article or outside the submitted work. TS receives investigator-initiated research funding and support as Principal Investigator (R01AG056479) from the National Institute on Aging (NIA), and as Co-Investigator (R01CA277756) from the National Cancer Institute, National Institutes of Health (NIH). He also receives salary support as Director of Comparative Effectiveness Research (CER), NC TraCS Institute, UNC Clinical and Translational Science Award (UM1TR004406), co-Director of the Human Studies Consultation Core, NC Diabetes Research Center (P30DK124723), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the Center for Pharmacoepidemiology (current members: GlaxoSmithKline, UCB BioSciences, Takeda, AbbVie, Boehringer Ingelheim, Astellas, and Sarepta), and from a generous contribution from Dr. Nancy A. Dreyer to the Department of Epidemiology, University of North Carolina at Chapel Hill. Dr. Stürmer does not accept personal compensation of any kind from any pharmaceutical company. He owns stock in Novartis, Roche, and Novo Nordisk.

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Received: 6 January 2025 / Accepted: 21 April 2025
Published online: 06 May 2025

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