Clinical Outcomes of ACE Inhibitors and ARBs in Older Adults More Than 85 Years after Acute Kidney Injury

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2025.10.03

Introduction

EDITORIAL

Angiotensin inhibition in patients with acute kidney injury: Dr. Jekyll or Mr. Hyde?

Michael Joannidis[1*] and Eric Hoste[2]

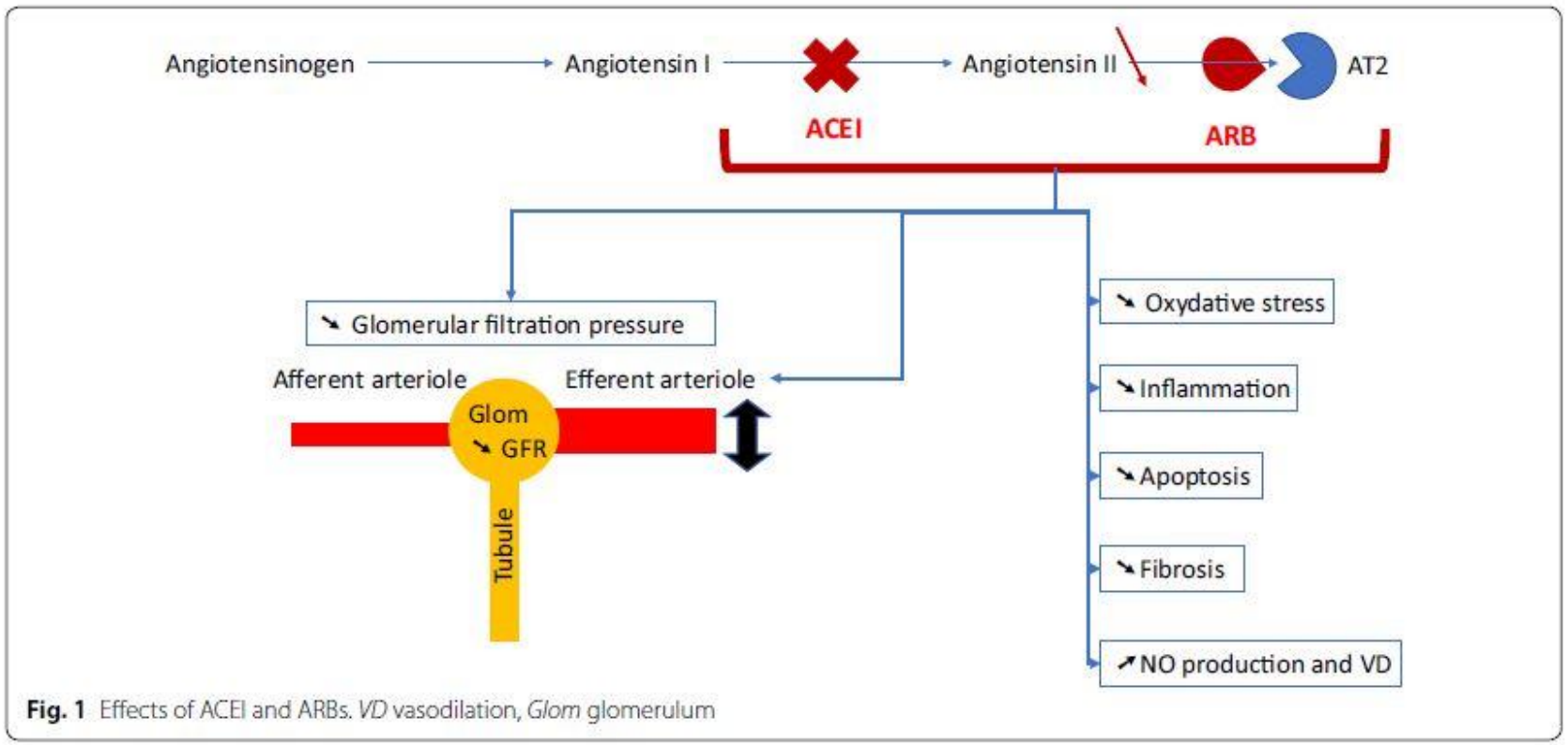
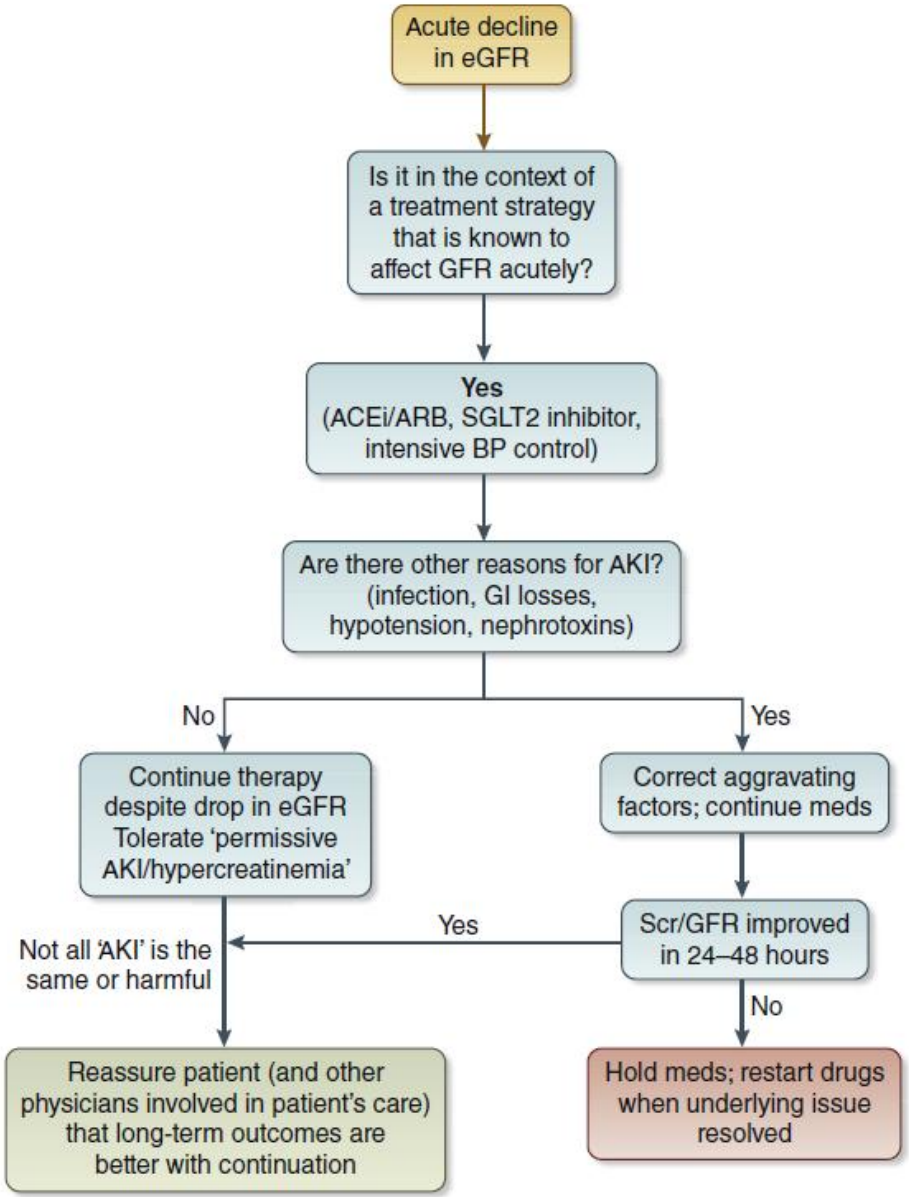


Fig. 1 Effects of ACEI and ARBs. *VD* vasodilation, *Glom* glomerulum

Intensive care Med. 2018 Jul;44(7):1159-1161.

"Permissive AKI" with treatment of heart failure

Chirag R. Parikh[1] and Steven G. Coca[2]



Parikh, C. R. et al. "Permissive AKI" with Treatment of Heart Failure. 2019. Kidney Int. 96 (5), 1066–1068

frontiers in Pharmacology

SYSTEMATIC REVIEW
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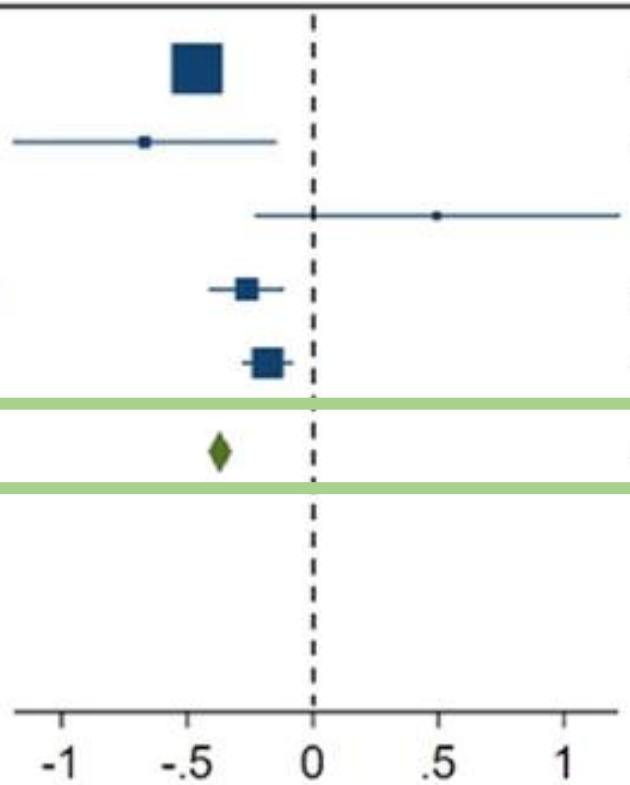
Check for updates

The Impact of Angiotensin-Converting Enzyme Inhibitors or Angiotensin II Receptor Blockers on Clinical Outcomes of Acute Kidney Disease Patients: A Systematic Review and Meta-Analysis

Jui-Yi Chen[1], *I-Jung Tsai*[2], *Heng-Chih Pan*[3,4], *Hung-Wei Liao*[5], *Javier A. Neyra*[6], *Vin-Cent Wu*[7,8] and *Jeff S. Chueh*[9,10]*

All-cause mortality

Study	Treatment Yes	Treatment No	Control Yes	Control No	Log Odds-Ratio with 95% CI	Weight (%)
Sandeep Brar-2018	3,713	5,743	4,781	4,675	-0.46 [-0.52, -0.40]	67.31
Etienne Gayat(2018)	20	89	153	349	-0.67 [-1.19, -0.15]	1.03
Mathilde Scarton (2019)	12	33	55	248	0.49 [-0.23, 1.22]	0.24
Yao Qiao(2020)	786	1,888	434	801	-0.26 [-0.41, -0.12]	9.72
Patrick Bidulka (2020)	941	2,914	1,460	3,778	-0.18 [-0.27, -0.08]	21.69
Overall					-0.37 [-0.42, -0.32]	

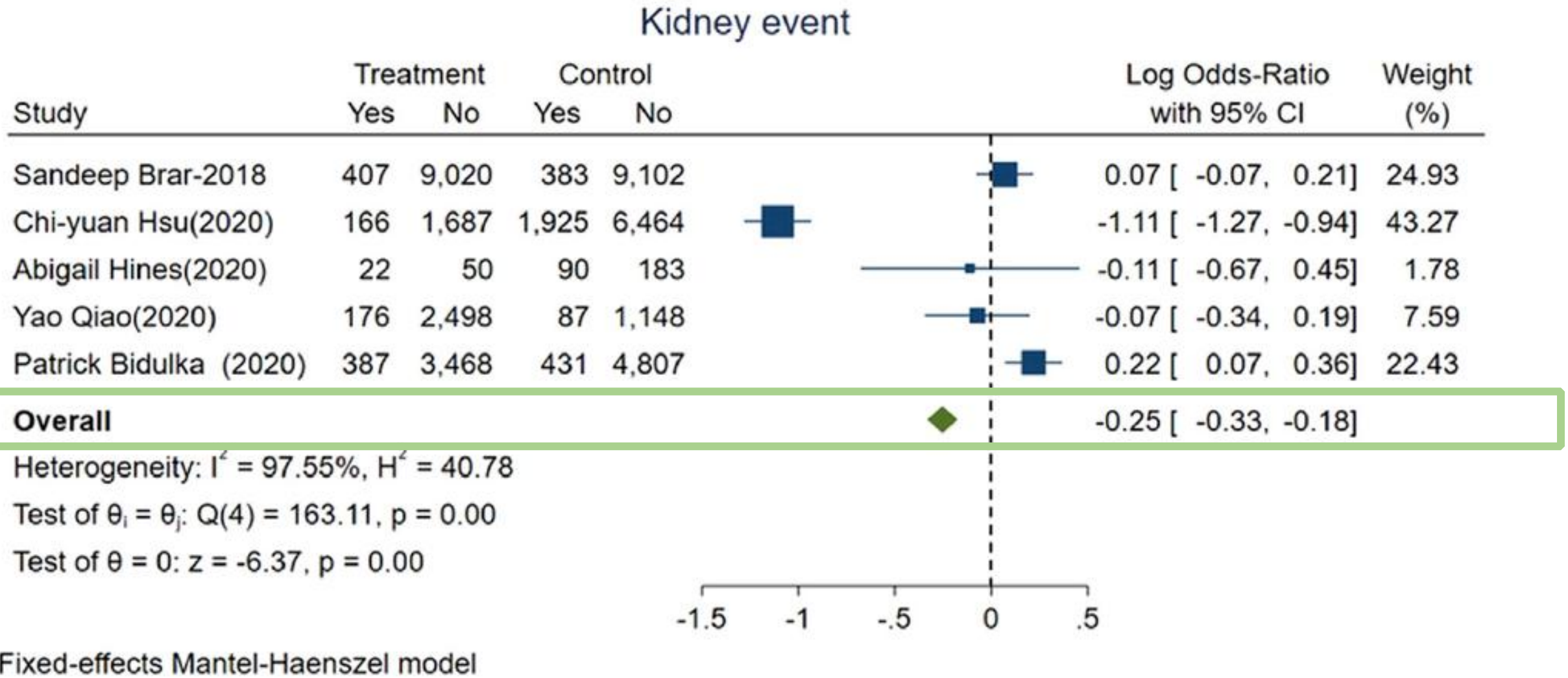


Heterogeneity: I^2 = 88.00%, H^2 = 8.33

Test of $\theta_i = \theta_j$: Q(4) = 33.32, p = 0.00

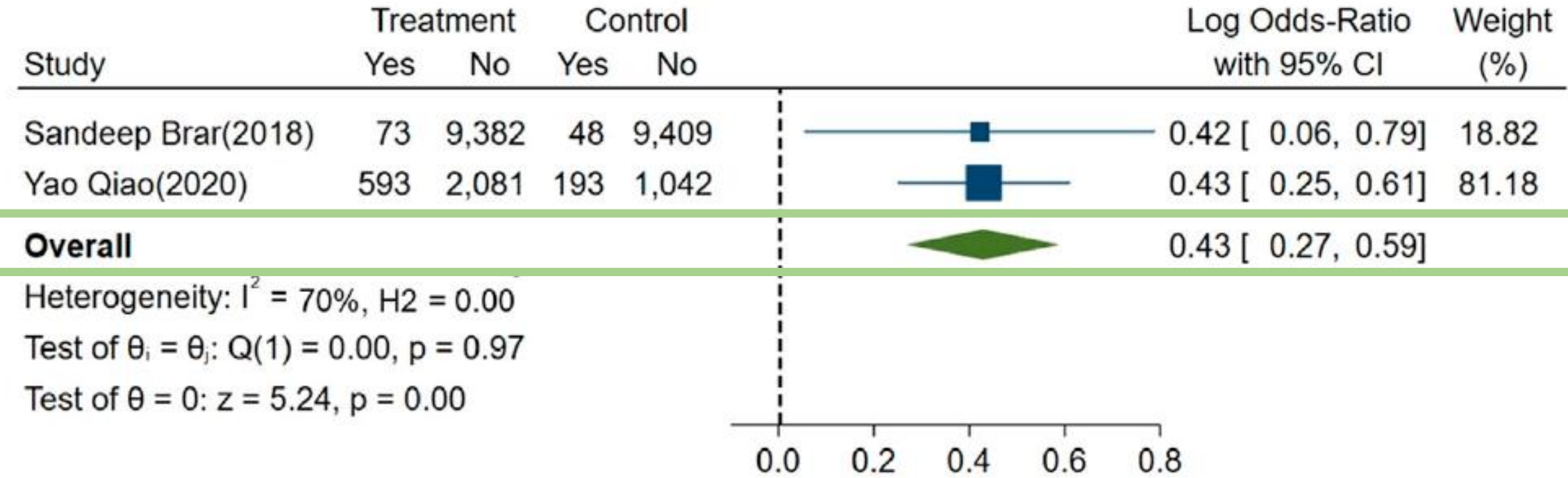
Test of θ = 0: z = -15.65, p = 0.00

Fixed-effects Mantel-Haenszel model



Kidney events, recurrent AKI or incident CKD or ESKD

Hyperkalemia



For CKD group

Practice Point 3.6.7:

Continue ACEi or ARB in people with CKD even when the eGFR falls below **30** ml/min per 1.73 m^2.

Navaneethan et al. KDOQI US Commentary on the KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of CKD. 2025. AJKD, 85(2)

The gap

- Data on the use of ACEi/ARB in very old patients, those over 85 years, following an episode of AKI remains scarce.

- growing aging population
- increasing prevalence of both AKI and CKD in this group
- the safety and clinical outcomes associated with ACEi/ARB is still unknown for this high-risk population

Methods

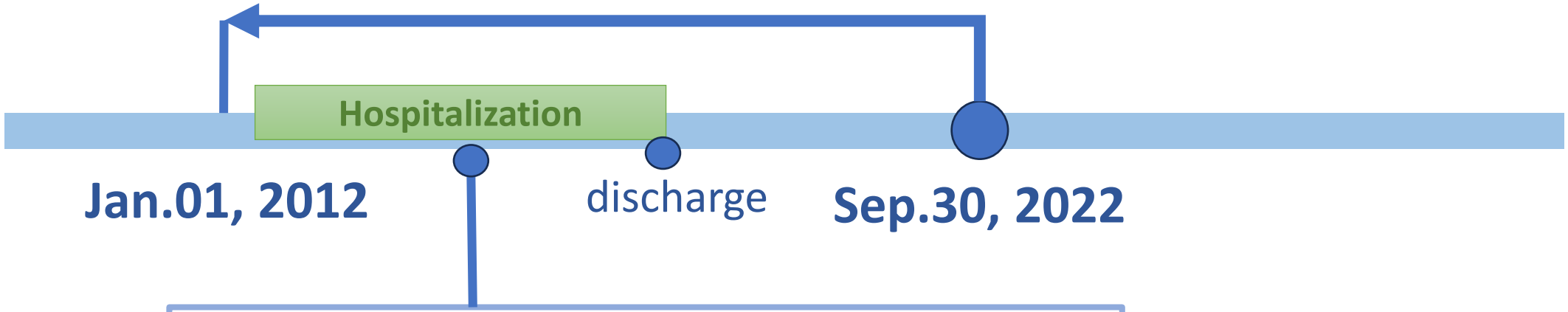
TriNetX Research Network

US Collaborative Network from 102 HCOs (healthcare organizations)

- Demographics
- Diagnosis (ICD-10-CM)
- Procedures CPT (Current Procedural Terminology)
- HCPCS (Healthcare Common Procedure Coding System)
- SNOMED (Systematized Nomenclature of Medicine - Clinical Terms), Comorbidities
- Medication, Laboratory tests, and Health care utilization.

4,214,969 hospitalized participants

683,678 >85 years old

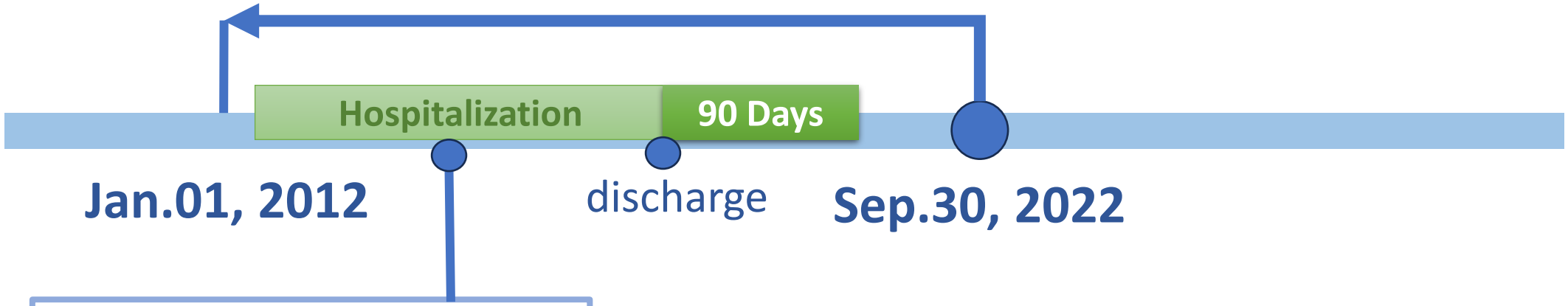


272,779

Ever dialysis for AKI during hospitalization and within 3 months before discharge.

4,214,969 hospitalized participants

683,678 >85 years old



Exclusion

130,374

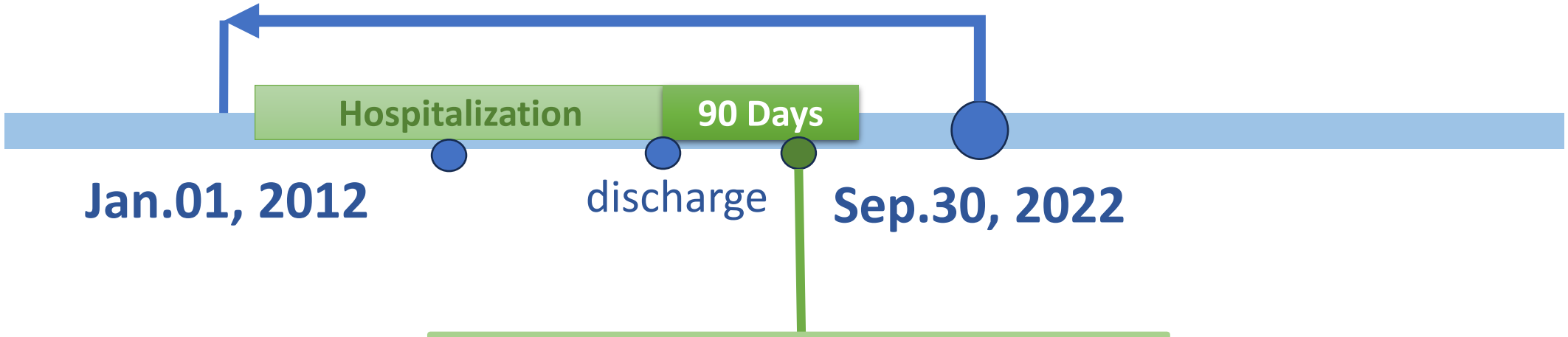
ACEi/ARB before discharge

27,943

Died during hospitalization

4,214,969 hospitalized participants

683,678 >85 years old

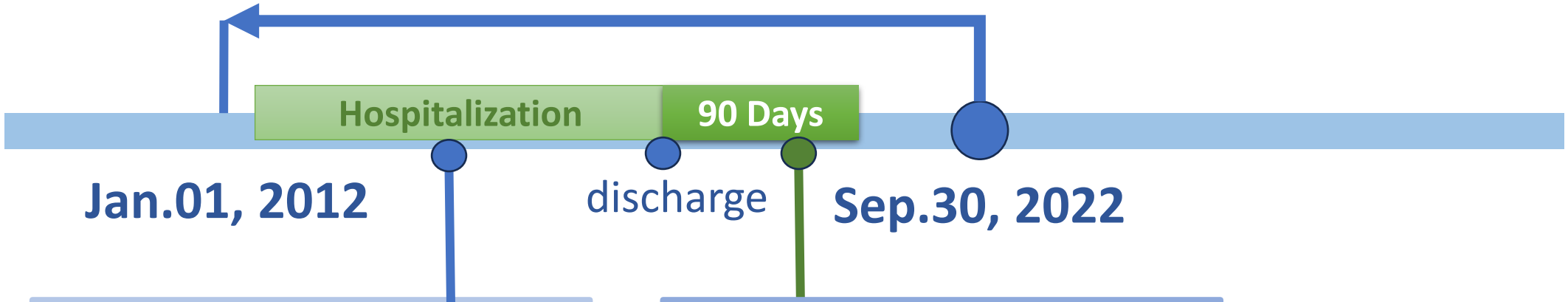


Selection period

- ACEi/ARB users/ Controls

4,214,969 hospitalized participants

683,678 >85 years old



Exclusion

130,374

ACEi/ARB before discharge

27,943

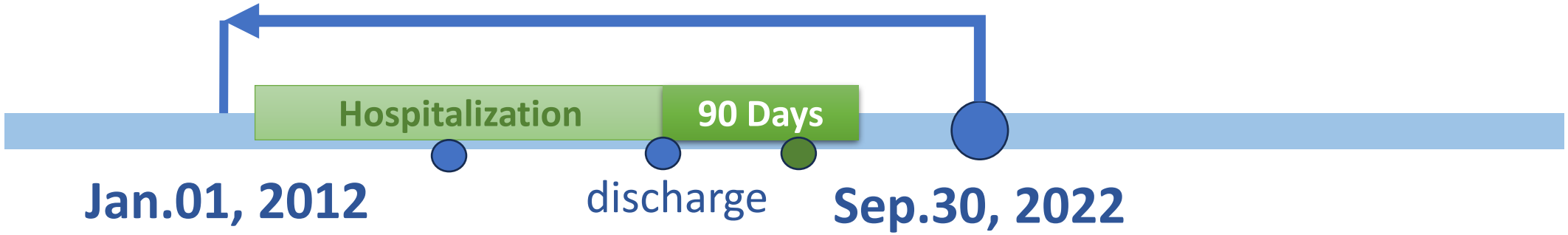
Died during hospitalization

Exclusion

1,100 Die

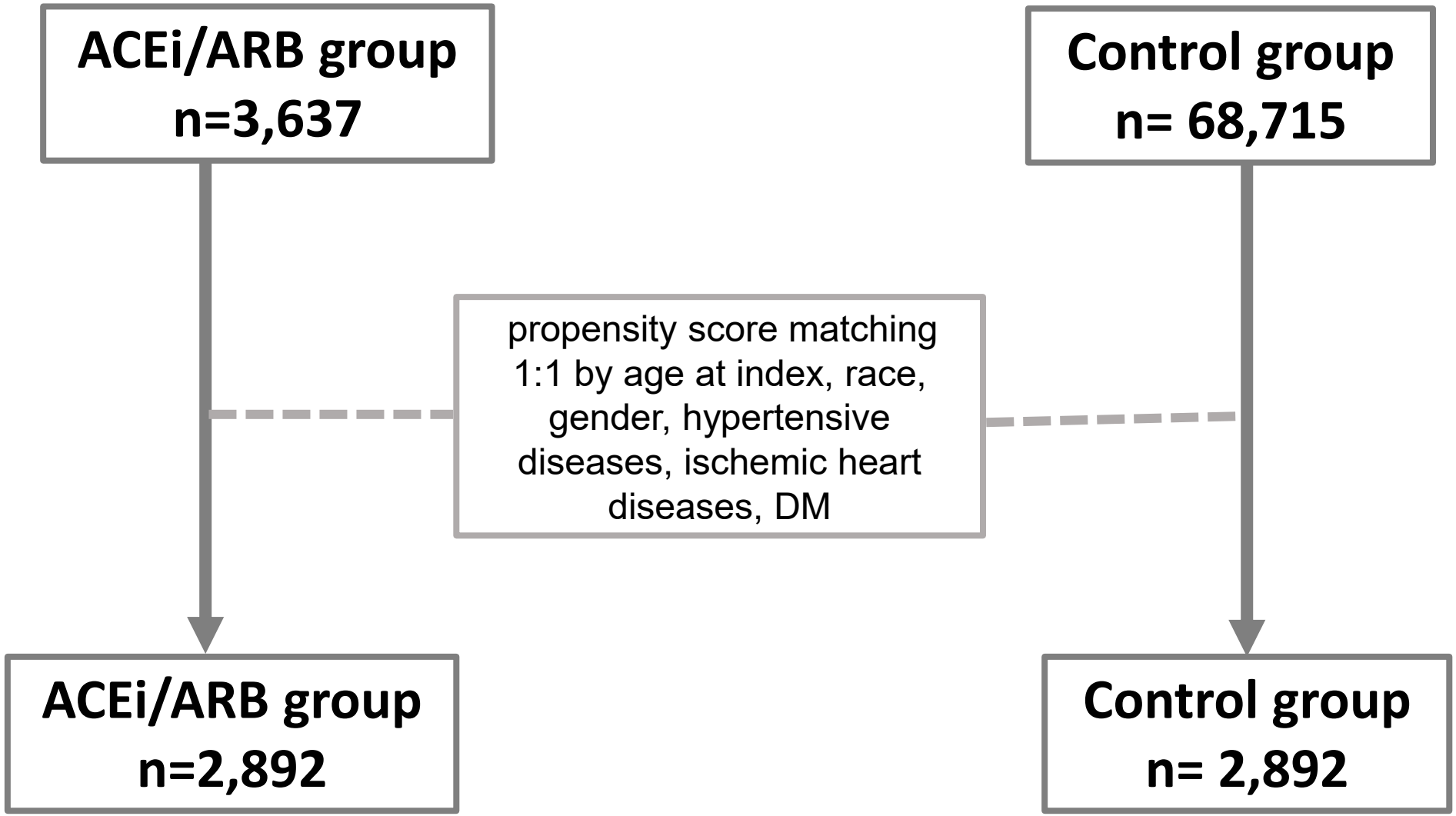
41,010

Dependent on dialysis



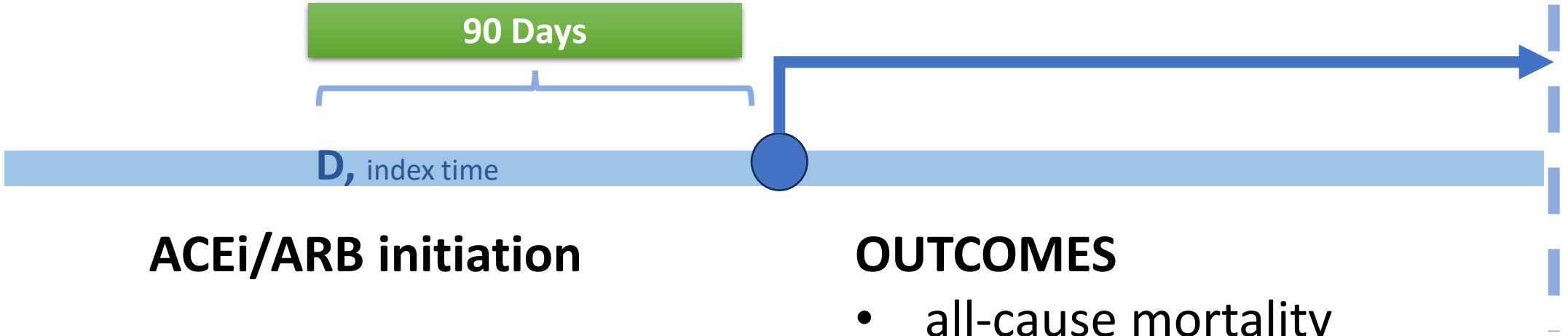
72,352

- AKI, requiring dialysis during hospitalization
- Discontinued dialysis after AKI and sustained 90 days


ACEi/ARB group
n=3,637
Control group
n= 68,715
propensity score matching
1:1 by age at index, race,
gender, hypertensive
diseases, ischemic heart
diseases, DM
ACEi/ARB group
n=2,892
Control group
n= 2,892

3 months

1 year



ACEi/ARB initiation

OUTCOMES

- all-cause mortality
- MAKE
- MACE

OUTCOMES

Main outcomes

- all-cause mortality

Secondary outcomes

- Major adverse kidney events (MAKE)
  death, CKD stage 5, or end-stage kidney disease (ESKD) requiring dialysis initiation
- Major adverse cardiac events (MACE)
  myocardial infarction, ischemic or hemorrhagic stroke, cardiac arrest, and cardiac death

OUTCOMES

Specific analysis

- Mortality or ESKD
- Mortality or dialysis
- Mortality or myocardial infarction,
- Mortality or stroke

Positive outcome: hypotension, hyperkalemia

Negative outcomes

traumatic brain injury and traffic accidents

OUTCOMES

Positive exposure control: statins v.s. placebo

Negative exposure control:

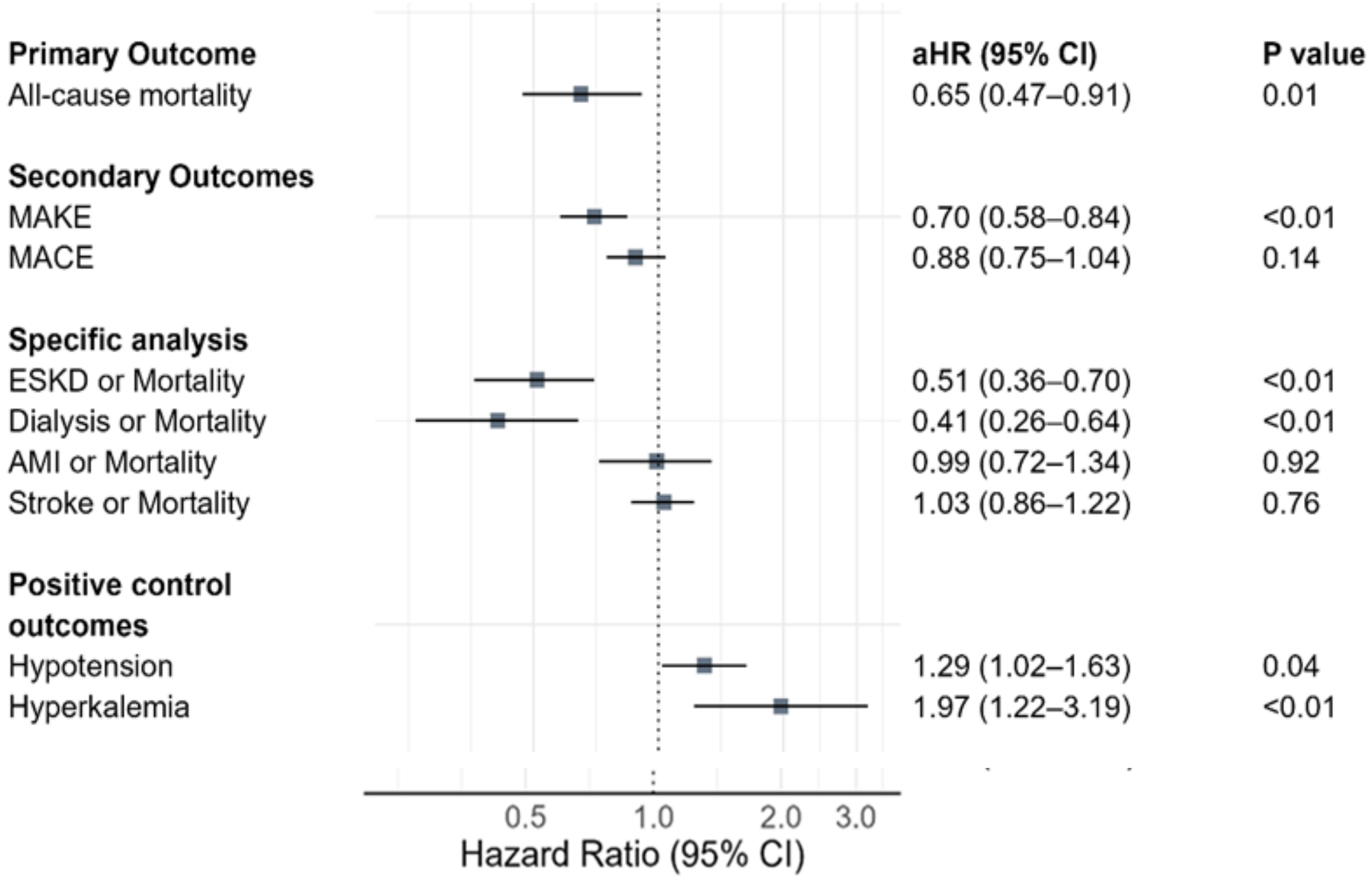
- Vit C v.s. placebo

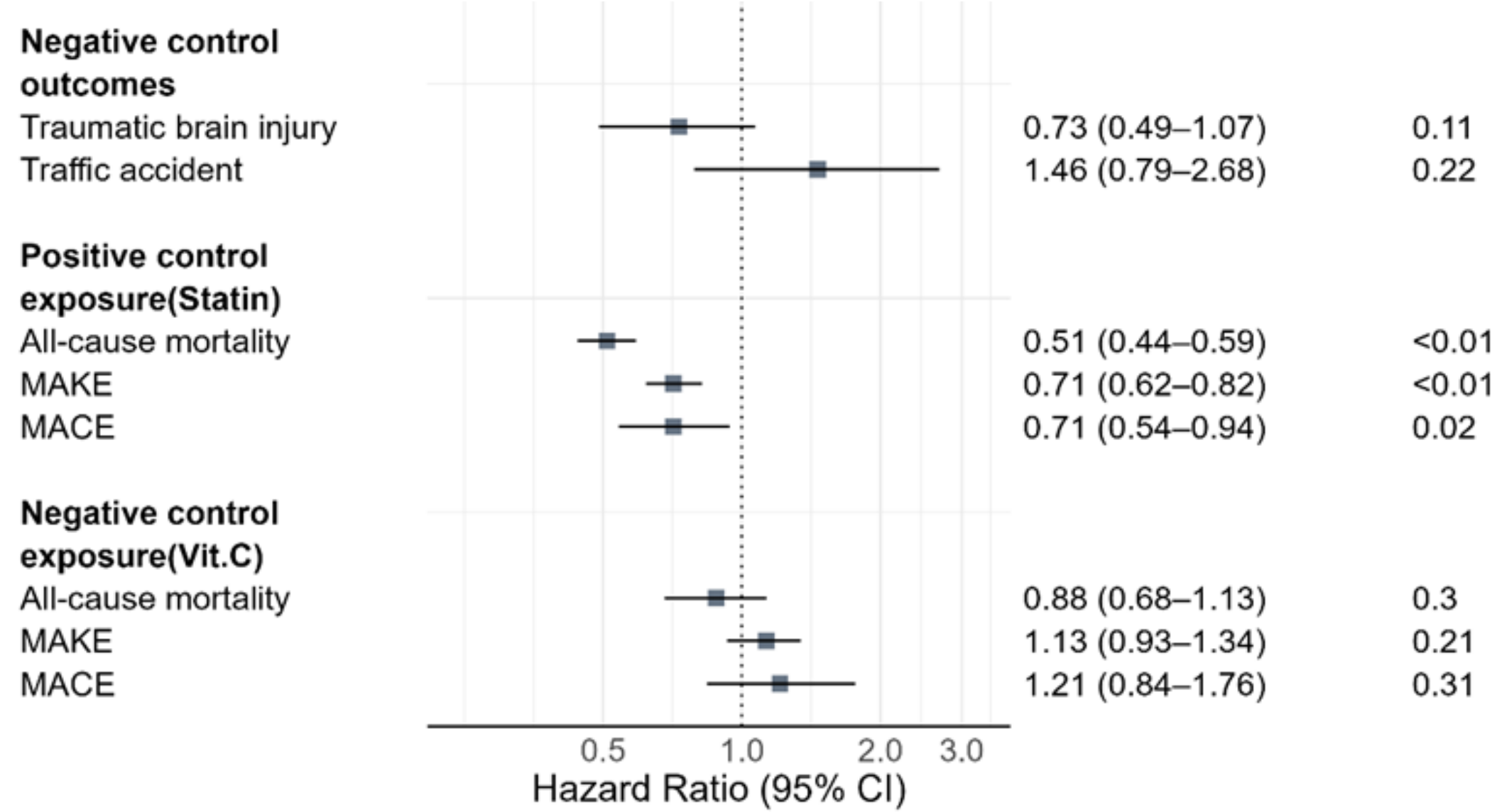
Results

Characteristics	Before matching			After matching		
	ACEi/ARB (n= 3,637)	Control (n=68,715)	Std. diff.	ACEi/ARB (n= 2,892)	Control (n= 2,892)	Std. diff.
Demographics						
Age (mean ± SD, year)	88.5 ± 1.8	88.8 ± 1.7	0.18	88.6 ± 1.8	88.7 ± 1.8	0.07
Male	1,347(40.0)	26,588(39.0)	0.02	1,157(40.0)	1,157(40.0)	<0.01
White	2,655(73.0)	49,544(72.1)	0.02	2,111(73.0)	2,030(70.2)	0.06
Asian	211(5.8)	4,947(7.2)	0.06	168(5.8)	223(7.71)	0.08
Black or African American	400(11.0)	6,459(9.4)	0.05	318(11.0)	289(10.0)	0.03
Unknown Race	262(7.2)	5,703(8.3)	0.04	208(7.2)	257(8.9)	0.06
Comorbidities						
Chronic kidney disease	2,051(56.4)	31,678(46.1)	0.21	1,631(56.4)	1,628(56.3)	<0.01
Hypertension	3,382(93.0)	49,406(71.9)	0.58	2,690(93.0)	2,684(92.8)	<0.01
Ischemic heart disease	1,855(51.0)	24,188(35.2)	0.32	1,475(51.0)	1,472(50.9)	<0.01
Diabetes mellitus	1,287(35.4)	16,766(24.4)	0.24	1,024(35.4)	1,006(34.8)	0.01

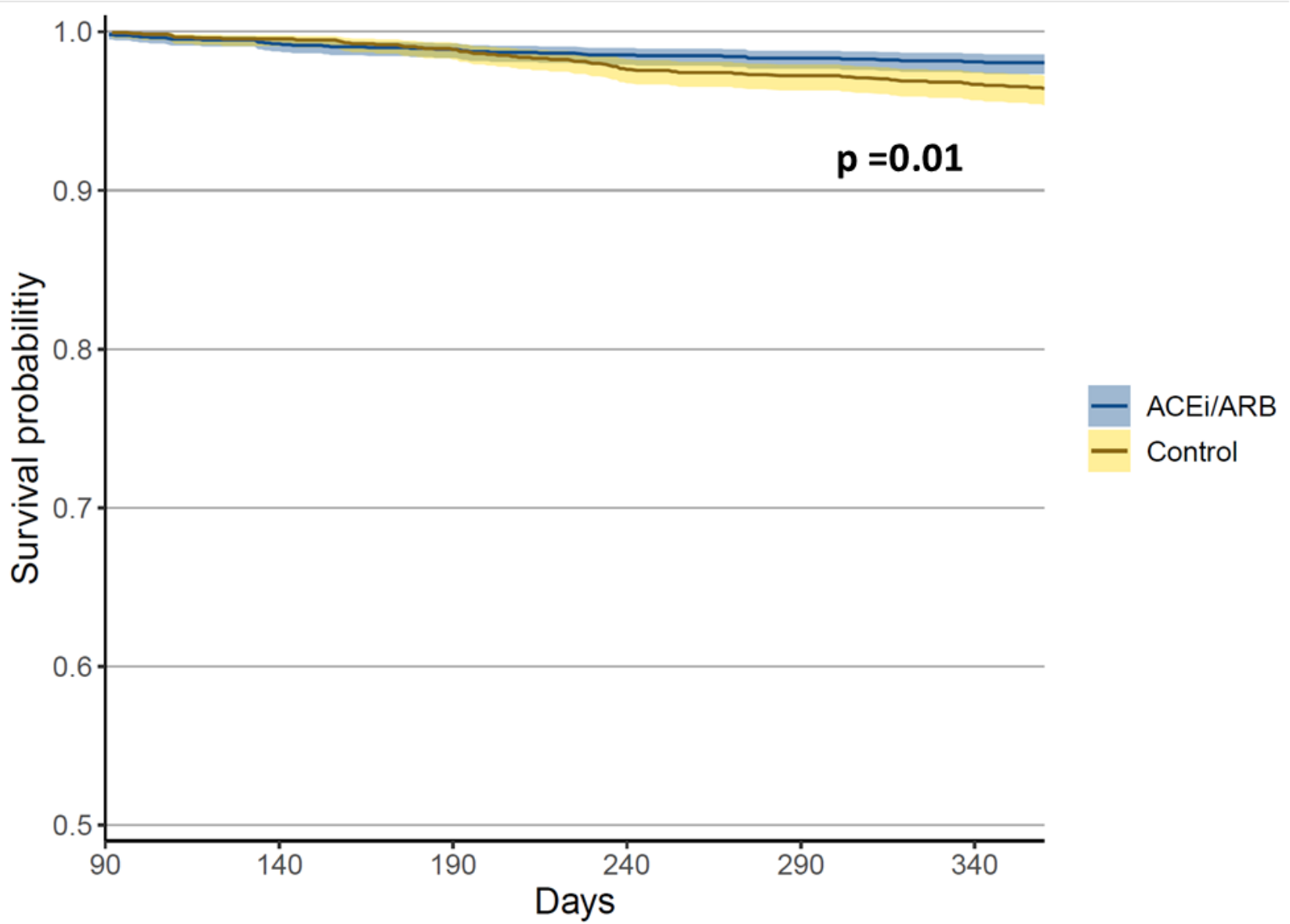
Characteristics	Before matching			After matching		
	ACEi/ARB (n= 3,637)	Control (n=68,715)	Std. diff.	ACEi/ARB (n= 2,892)	Control (n= 2,892)	Std. diff.
Medications						
Antiarrhythmics	2,342(64.4)	36,831(53.6)	0.23	1,865(64.5)	1,891(65.4)	0.02
Diuretics	2,642(67.7)	29,685(43.2)	0.53	1,961(67.8)	2,013(69.6)	0.04
Insulin	1,335(36.7)	18,965(27.6)	0.23	1,064(36.8)	1,058(36.6)	<0.01
Oral hypoglycemic agents	775(21.3)	5,016(7.3)	0.42	616(21.3)	628(21.7)	<0.01
Beta blockers	2,666(73.3)	37,106(54.0)	0.43	2,123(73.4)	2,178(75.3)	0.05
CCB	1,928(53.0)	23,363(34.0)	0.40	1,536(53.1)	1,544(53.4)	<0.01

Characteristics	Before matching			After matching		
	ACEi/ARB (n= 3,637)	Control (n=68,715)	Std. diff.	ACEi/ARB (n= 2,892)	Control (n= 2,892)	Std. diff.
Laboratory tests						
Creatinine (mg/dL)	76.9 ± 33.0	74.4 ± 32.3	0.07	76.9 ± 33.0	80.2 ± 34.9	0.02
Hb >12 g/dL	2,913(80.1)	45,489(66.2)	0.32	2,322(80.3)	2,369(81.9)	0.02
Total bilirubin (mg/dL)	0.7 ± 0.6	0.8 ± 1.4	0.09	0.7 ± 0.6	0.74 ± 1.0	0.07
Glycated hemoglobin (%)	6.2 ± 1.5	6.2 ± 1.5	<0.01	6.2 ± 1.5	6.2 ± 1.5	<0.01
LDL (mg/dl)	84.7 ± 35.8	87.0 ± 38.1	0.06	84.7 ± 35.8	83.7 ± 36.4	0.03
BMI (kg/m^2)	26.6 ± 5.6	25.1 ± 5.7	0.26	26.6 ± 5.6	26.4 ± 6.3	0.03

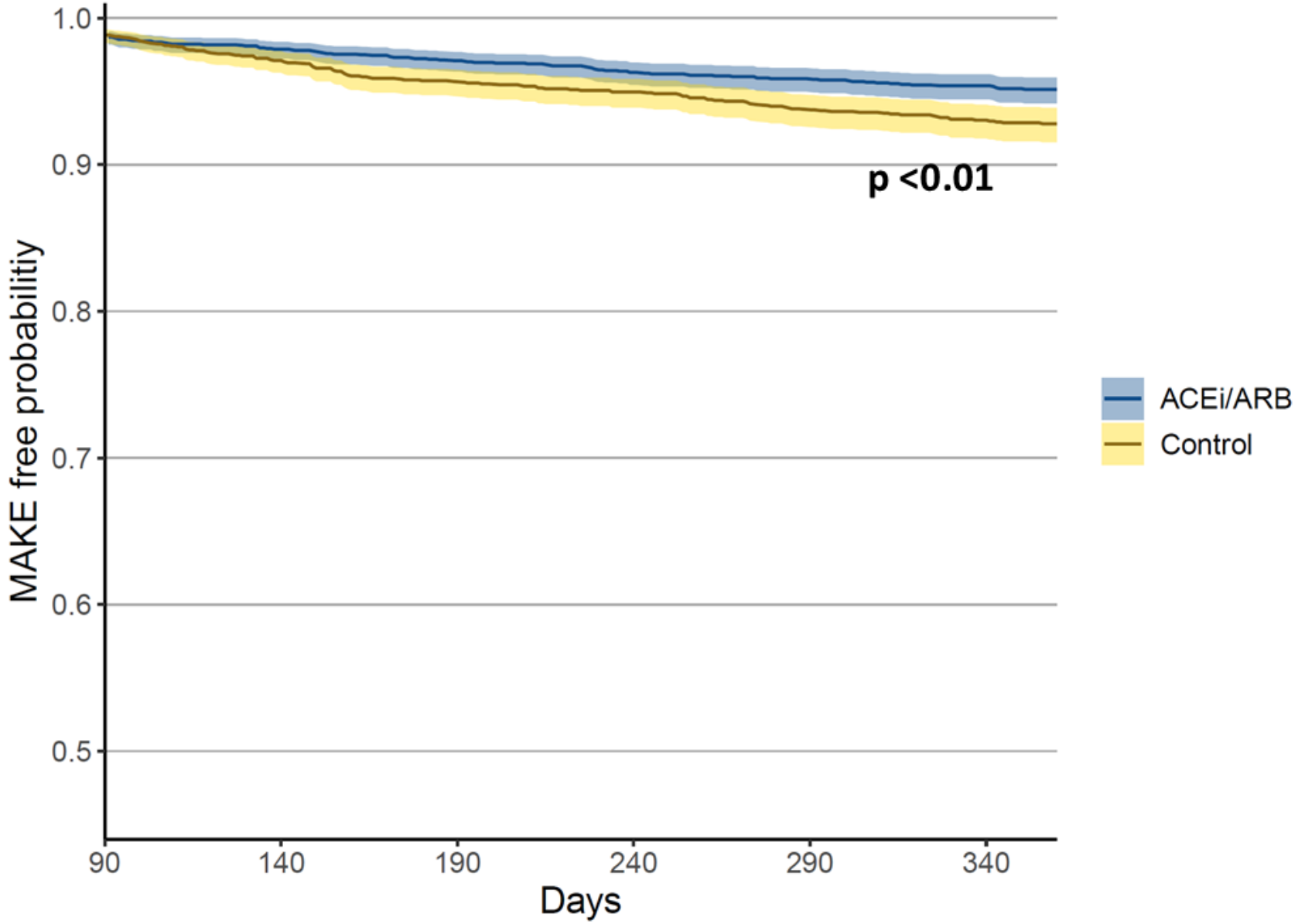

Primary Outcome
All-cause mortality
aHR (95% CI)
0.65 (0.47–0.91)
P value
0.01
Secondary Outcomes
MAKE
0.70 (0.58–0.84)
<0.01
MACE
0.88 (0.75–1.04)
0.14
Specific analysis
ESKD or Mortality
0.51 (0.36–0.70)
<0.01
Dialysis or Mortality
0.41 (0.26–0.64)
<0.01
AMI or Mortality
0.99 (0.72–1.34)
0.92
Stroke or Mortality
1.03 (0.86–1.22)
0.76
Positive control outcomes
Hypotension
1.29 (1.02–1.63)
0.04
Hyperkalemia
1.97 (1.22–3.19)
<0.01
0.5
1.0
2.0
3.0
Hazard Ratio (95% CI)


Negative control outcomes
Traumatic brain injury
Traffic accident
0.73 (0.49–1.07)
0.11
1.46 (0.79–2.68)
0.22
Positive control exposure(Statin)
All-cause mortality
MAKE
MACE
0.51 (0.44–0.59)
<0.01
0.71 (0.62–0.82)
<0.01
0.71 (0.54–0.94)
0.02
Negative control exposure(Vit.C)
All-cause mortality
MAKE
MACE
0.88 (0.68–1.13)
0.3
1.13 (0.93–1.34)
0.21
1.21 (0.84–1.76)
0.31
0.5
1.0
2.0
3.0
Hazard Ratio (95% CI)

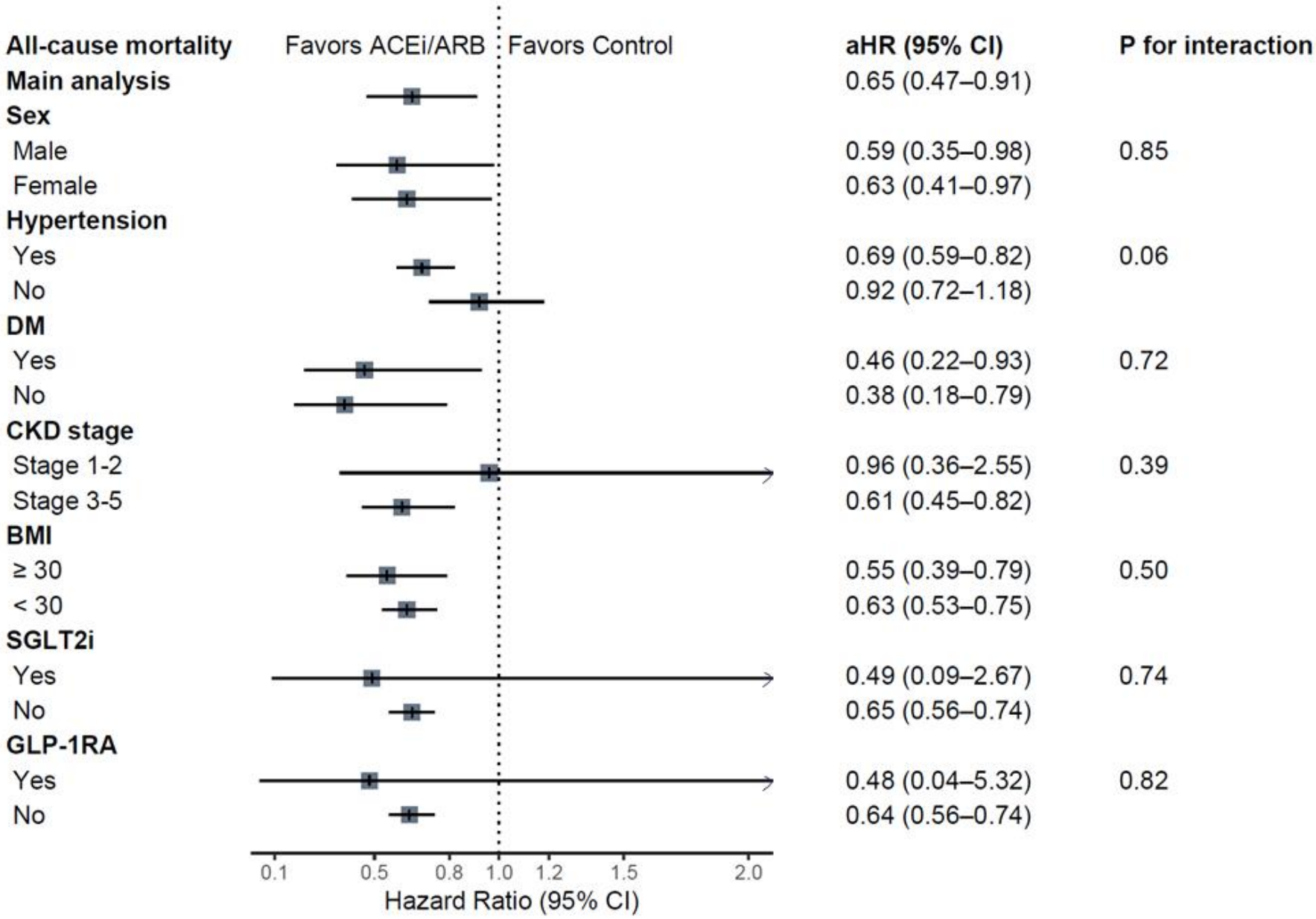
All-cause mortality



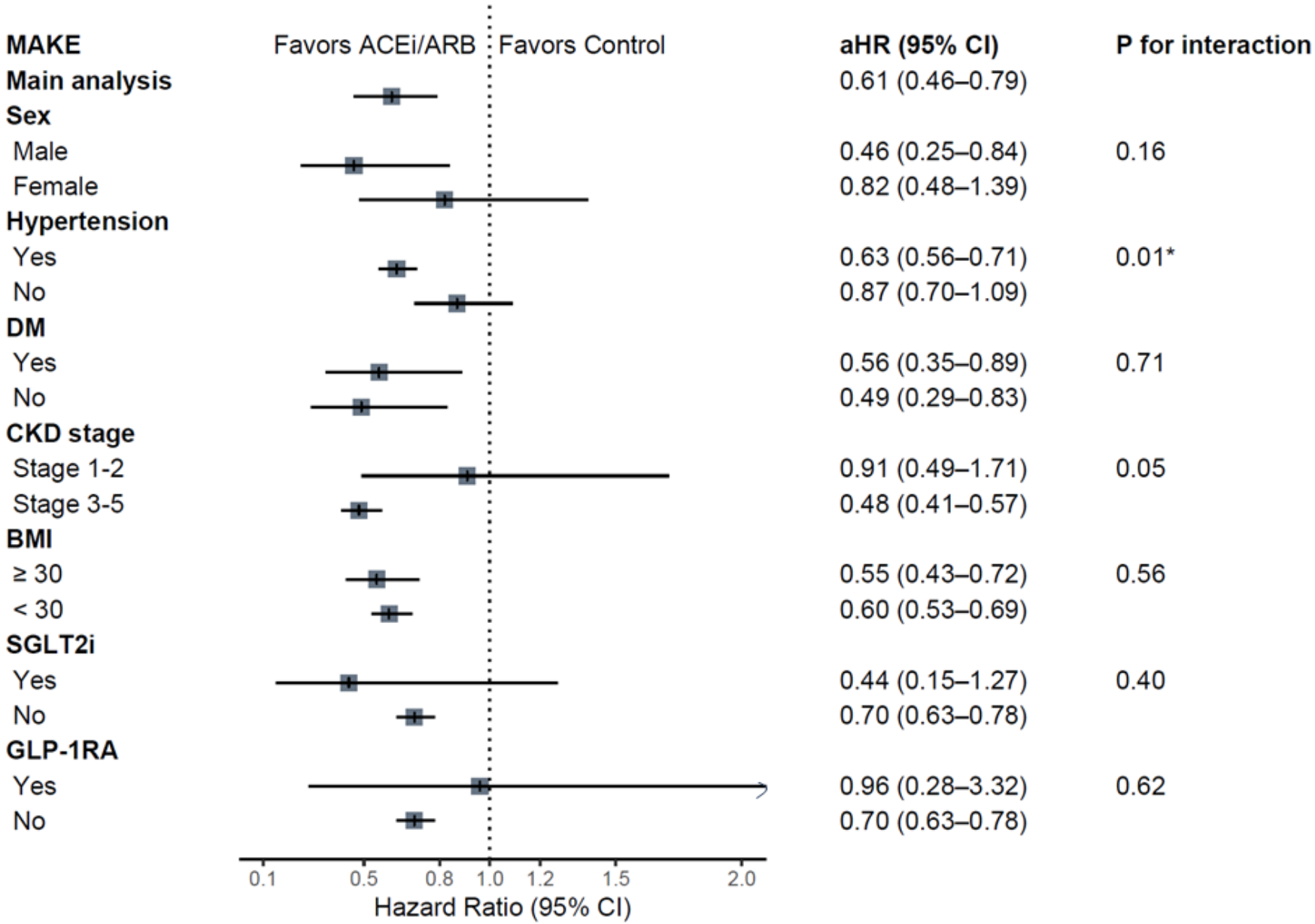
MAKE


1.0
0.9
0.8
0.7
0.6
0.5
MAKE free probabilitiy
p <0.01
90
140
190
240
290
340
Days
ACEi/ARB
Control

All-cause mortality



MAKE


MAKE
Favors ACEi/ARB
Favors Control
aHR (95% CI)
P for interaction
Main analysis
0.61 (0.46–0.79)
Sex
Male
0.46 (0.25–0.84)
0.16
Female
0.82 (0.48–1.39)
Hypertension
Yes
0.63 (0.56–0.71)
0.01*
No
0.87 (0.70–1.09)
DM
Yes
0.56 (0.35–0.89)
0.71
No
0.49 (0.29–0.83)
CKD stage
Stage 1-2
0.91 (0.49–1.71)
0.05
Stage 3-5
0.48 (0.41–0.57)
BMI
≥ 30
0.55 (0.43–0.72)
0.56
< 30
0.60 (0.53–0.69)
SGLT2i
Yes
0.44 (0.15–1.27)
0.40
No
0.70 (0.63–0.78)
GLP-1RA
Yes
0.96 (0.28–3.32)
0.62
No
0.70 (0.63–0.78)
0.1
0.5
0.8
1.0
1.2
1.5
2.0
Hazard Ratio (95% CI)

Discussion

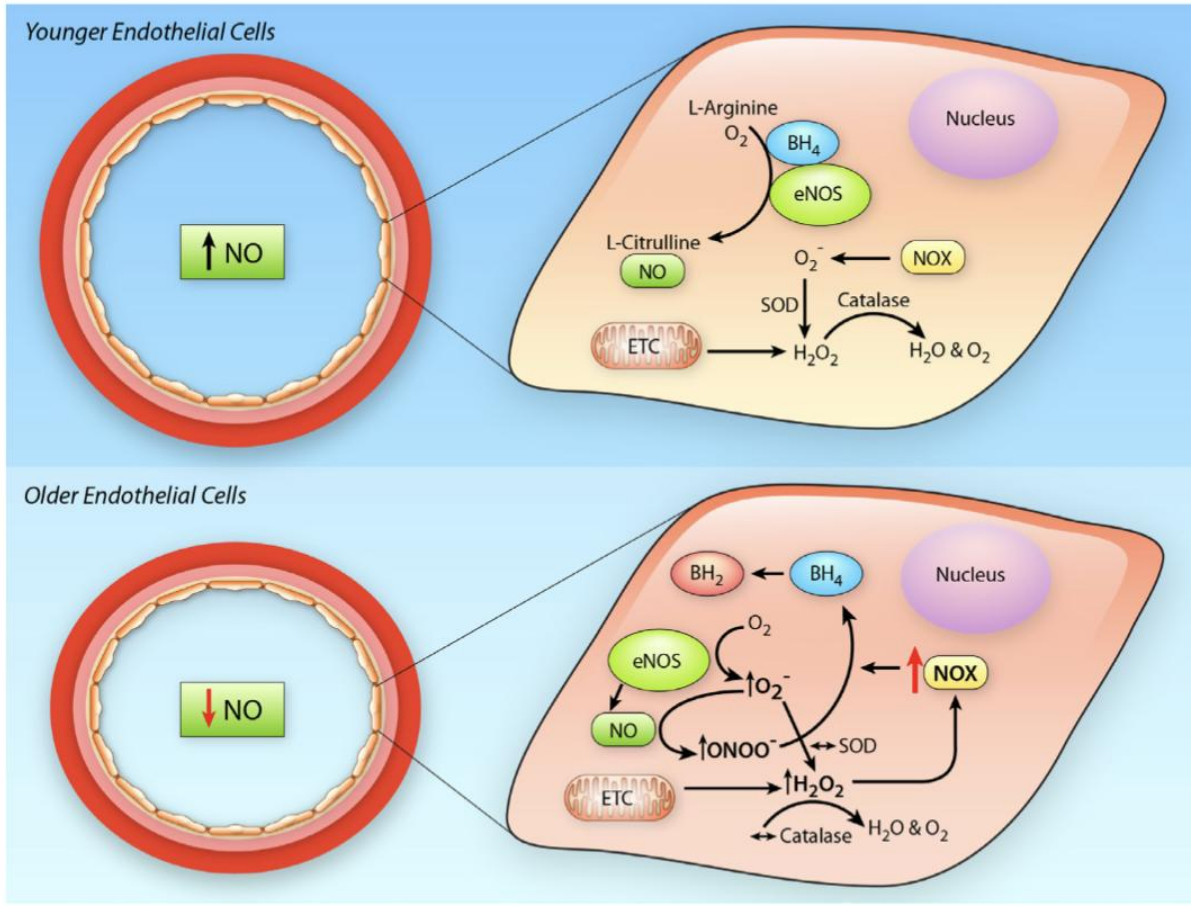
Table 2. Correlates of ACE-Inhibitor or ARB Use in 21,138 Patients With a Diagnosis of Hypertension or Proteinuria

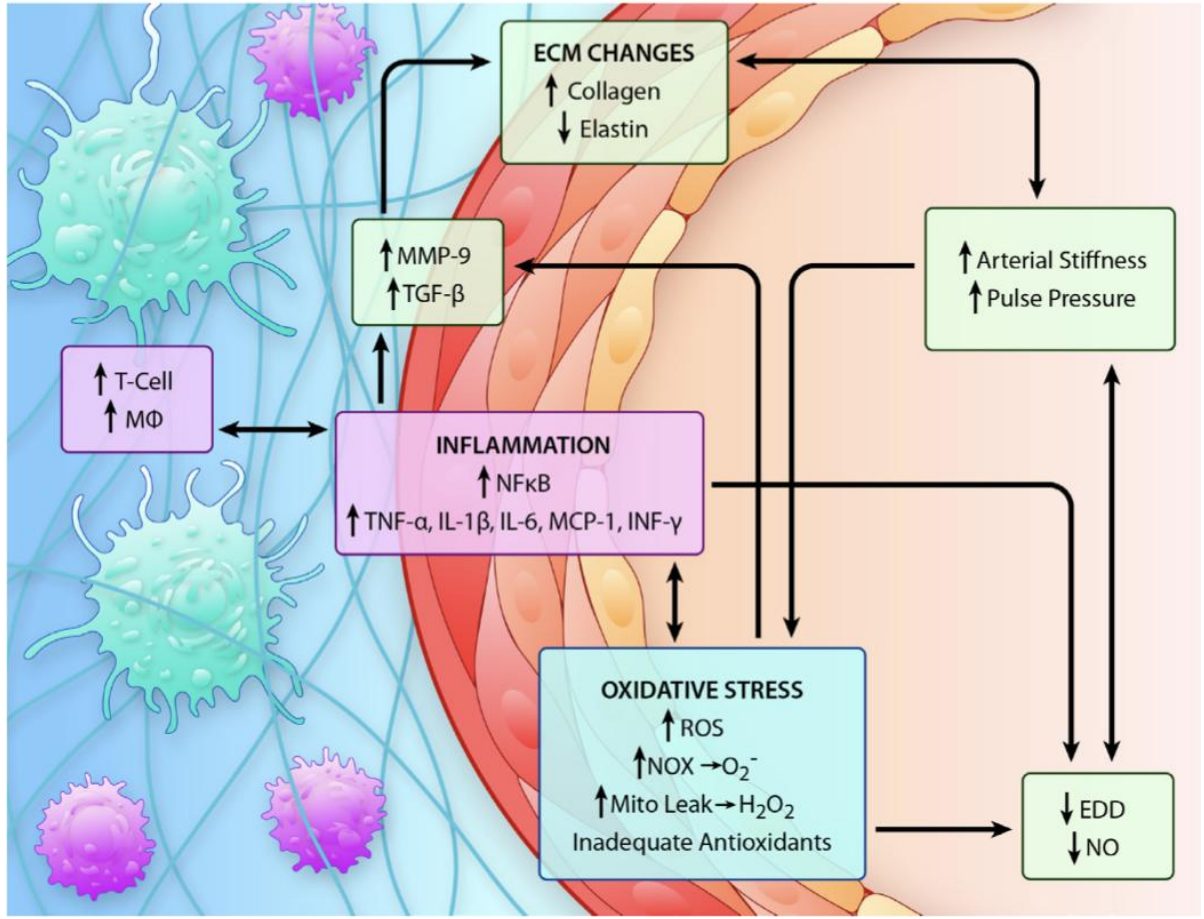
	Univariate			Multivariate		
Variable	OR	95% CI	*P*	OR	95% CI	*P*
Age (y)						
65-74	1.0	Referent	—	1.0	Referent	—
75-84	0.94	0.88-1.00	0.04	0.92	0.86-0.98	0.01
≥85	0.72	0.66-0.78	<0.001	0.70	0.65-0.76	<0.001

Winkelmayer WC, et al. Underuse of ACE inhibitors and angiotensin II receptor blockers in elderly patients with diabetes. Am J Kidney Dis 2005; 46: 1080-7.

Limited use of ACEi/ARB for older populations

- age-related frailty
- limited prognosis
- possible adverse events (kidney function declining)





Endothelial dysfunction

Oxidative stress

Donato AJ, Machin DR, Lesniewski LA. Mechanisms of Dysfunction in the Aging Vasculature and Role in Age-Related Disease. Circ Res 2018; 123: 825-48.

Benefits of ACEi/ARB

- ACEi/ARB have been shown to reduce inflammation and oxidative stress, further contributing to their beneficial effect

Brown NJ, Vaughan DE. Angiotensin-converting enzyme inhibitors. Circulation 1998; 97: 1411-20.

Benefits of ACEi/ARB

- ACEi/ARB therapy may attenuate maladaptive post-AKI responses,
  - persistent glomerular hypertension
  - interstitial fibrosis
  - inflammation,

  which are more pronounced in aging kidneys.

Brar S, et al. Association of Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker Use With Outcomes After Acute Kidney Injury. JAMA Intern Med 2018; 178: 1681-90.

Risk of hypotension and hyperkalemia

- The most common causes of AKI in this age group include
  - ✓ volume depletion
  - ✓ dehydration
  - ✓ reduced renal perfusion, which are often multifactorial in origin, such as hypotension, sepsis, or diuretic overuse

Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. Am J Kidney Dis 2002; 39: 930-6.

Limitations

- residual confounding from unmeasured covariates and potential misclassifications
- short follow-up duration may have limited our ability to observe long-term cardiovascular outcomes
- several risk factors for mortality
  - ✓ Frailty
  - ✓ functional status
  - ✓ medication adherence

  were not available from the dataset.

Conclusion

adults aged over 85 years who survived dialysis for AKI during hospitalization, the ACEi/ARB therapy

- lower risk of all-cause mortality and major adverse kidney events
- the higher risks of hypotension and hyperkalemia

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SAVE THE DATES

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Update in AKI Medicine:
Controversies, Challenges and Solutions

Sep. 18 (Fri.) - 20 (Sun.), 2026

Taipei Marriott Hotel, Taipei, Taiwan

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ACEi/ARB vs CCB