Renin-angiotensin system blockers and susceptibility to COVID-19: an international open science cohort study

Marc A Suchard, MD PhD, on behalf of
the ICARIUS team

Background and Call for Evidence

Authors	COVID Patients	Location	Key Content
Guan et al	1099	China	24% HTN in severe disease (vs 13% overall)
Zhou et al	191	China	HTN Univariate OR 3.1 (1.6-6.0) for death

- People with hypertension (HTN) have worse COVID-19 outcomes
- Speculation that ACEi/ARBs taken for HTN may be detrimental
  - Coronaviruses interact with RAS ACE-2 receptor, allowing them to enter the cell
- Speculation that ARBs may be protective
  - Prevent the angiotensin I receptor from being stimulated

HFSA/ACC/AHA Statement Addresses Concerns Re: Using RAAS Antagonists in COVID-19

Mar 17, 2020

AMERICAN COLLEGE of CARDIOLOGY

HFSA HEART FAILURE SOCIETY OF AMERICA

American Heart Association

ESC European Society of Cardiology

Position Statement of the ESC Council on Hypertension on ACE-Inhibitors and Angiotensin Receptor Blockers

13 Mar 2020

Precisazioni AIFA su Malattia da coronavirus Covid-19 ed utilizzo di ACE-Inibitori e Sartani

AIFA AGENZIA ITALIANA DEL FARMACO

Clinical Hypotheses

1. **Prevalent ACEi or ARB use is associated with a difference in risk of COVID-19 infection relative to an active comparator in hypertensive patients**

2. Prevalent ACEi or ARB use in COVID-19+ patients is associated with a difference in risk of intensive outcomes relative to an active comparator in hypertensive patients
    - This work is still in progress and will not be included in this presentation

Research Network Data Partners

Data sources	Country / sample size	Data elements
Information Systems for Research in Primary Care (SIDIAP) database	Spain ≈ 6 million	**GP EHR linked to hosp admits** Dx, Rx, labs, demographics, COVID-19 tests/Dx
US Department of Veterans Affairs (VA) database	U.S. ≈ 12 million	**Linked administrative claims** Dx, Rx, labs, lifestyle, sociodemographics, COVID-19 tests/Dx
Columbia University Irving Medical Center data warehouse (CUIMC)*	U.S. (NYC) ≈ 6 million	**Health-system EHR** Dx, Rx, labs, demographics, COVID-19 tests/Dx,

** Analyses implemented in CUIMC did not pass a priori diagnostic assessments. Thus, this presentation includes only limited description of those analyses and findings.*

1000s of hours of dedication

Team SIDIAP

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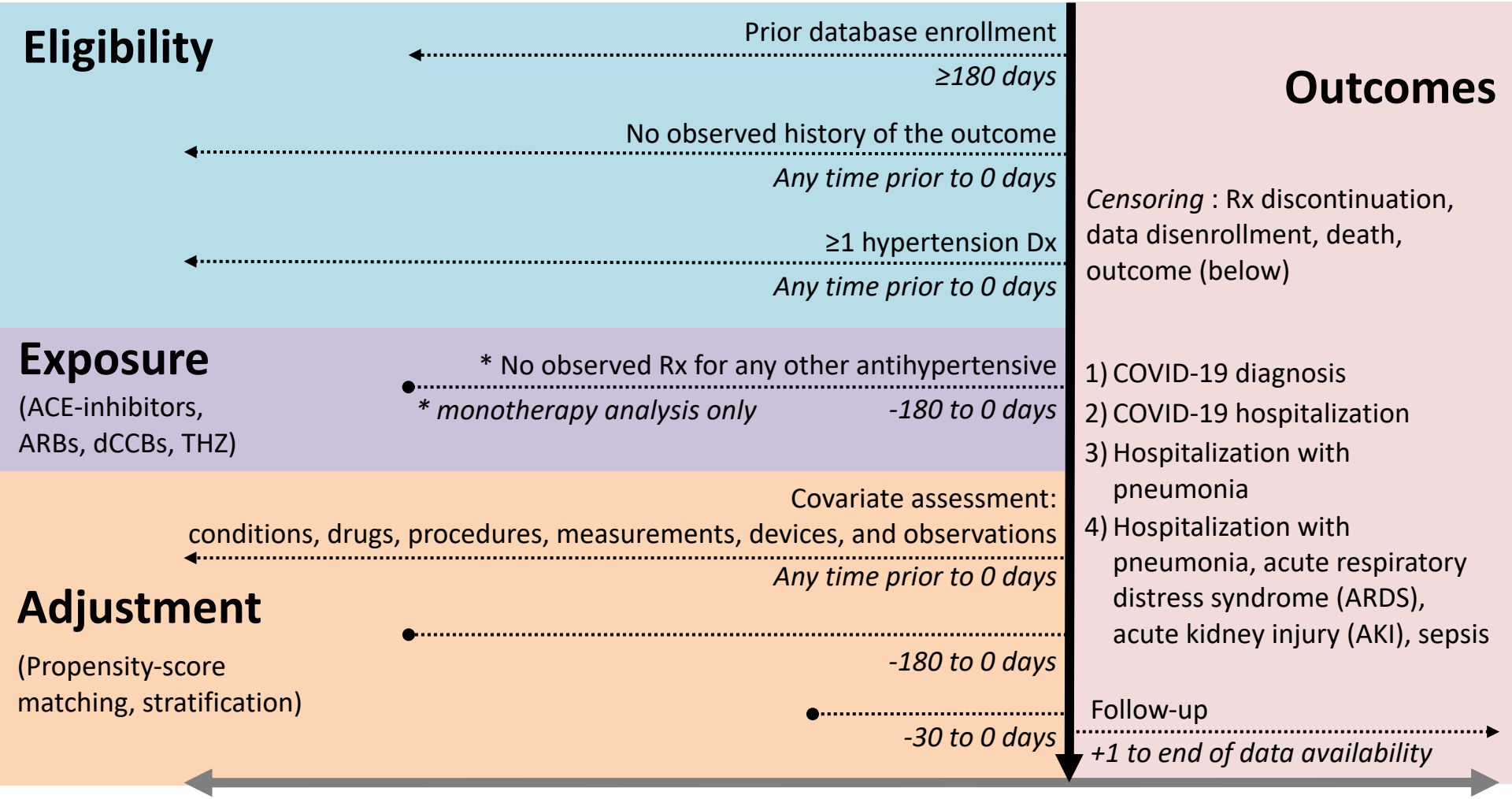
Team VA

- Scott DuVall

- Aize Cao
- Kristine Lynch
- Michael Matheny

Study Schematic



** It is not possible for patients to meet criteria to enter both target and comparator cohorts*

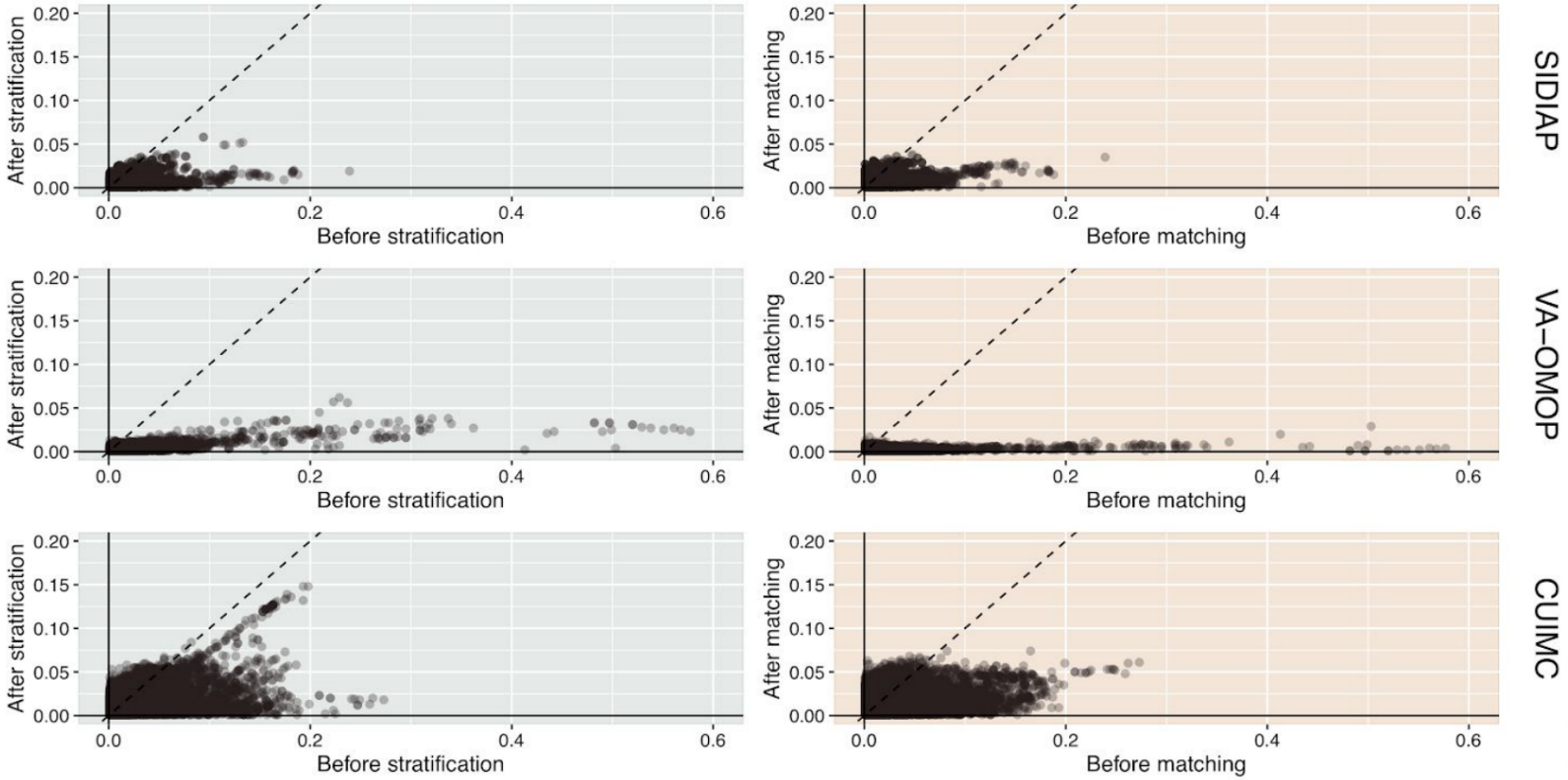
Statistical Methods

- Large-scale propensity-score (PS) models selected using a data-driven regularized regression approach
- Balanced covariates using two PS approaches:
  - 1:N variable-ratio PS-matching
  - PS stratification using 5 quintiles
- Estimated hazard ratios (HRs) using cox proportional hazards models
  - Conditioned on PS strata or matching unit
- Empirical calibration using up to 123 negative controls
  - Negative control outcomes identified using a data-rich algorithm
  - Calibrated each HR estimate and 95% CI using the empirical null distributions
- These analyses do not statistically account for multiple testing

Patient and event counts

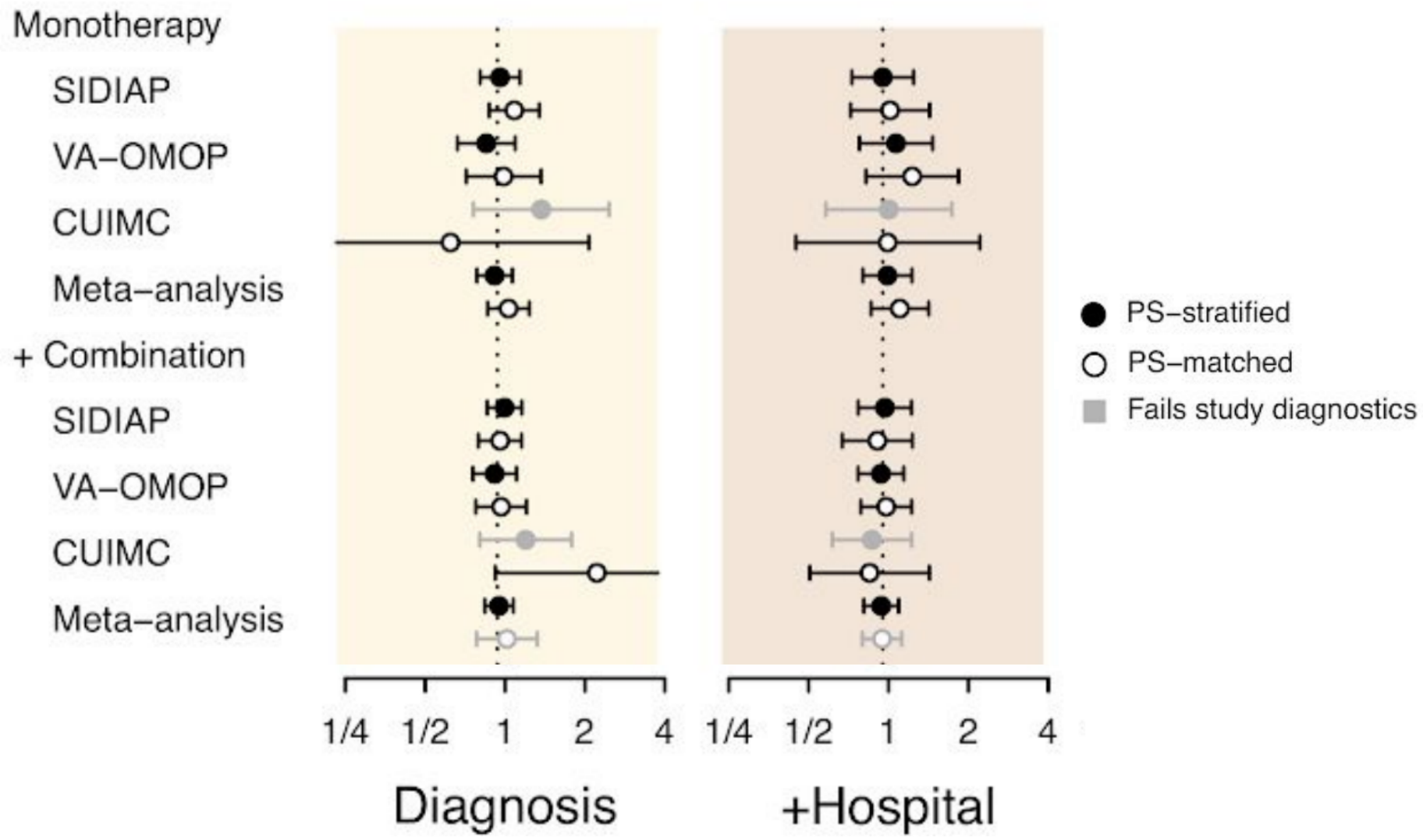
	SIDIAP (Spain)				VA (U.S.)			
	Patients		Events		Patients		Events	
	T	C	T	C	T	C	T	C
ACE/ARB vs CCB/THZ								
Monotherapy	37,796	14,003	500	184	320,450	229,063	145	183
Combo therapy	45,239	19,007	627	250	656,274	443,061	345	335
ACE vs CCB/THZ								
Monotherapy	30,787	14,003	398	184	235,348	229,063	96	183
Combo therapy	36,323	29,239	485	399	457,557	639,500	218	494
ARB vs. CCB/THZ								
Monotherapy	6,753	14,003	95	184	82,872	229,063	46	183
Combo therapy	9,194	39,427	137	519	201,503	854,224	127	574
ACE vs. ARB								
Monotherapy	30,787	6,753	398	95	235,348	82,872	96	46
Combo therapy	56,465	19,148	758	283	865,931	395,156	441	282

Baseline covariate balance: ACE/ARB vs. CCB/THZ monotherapy

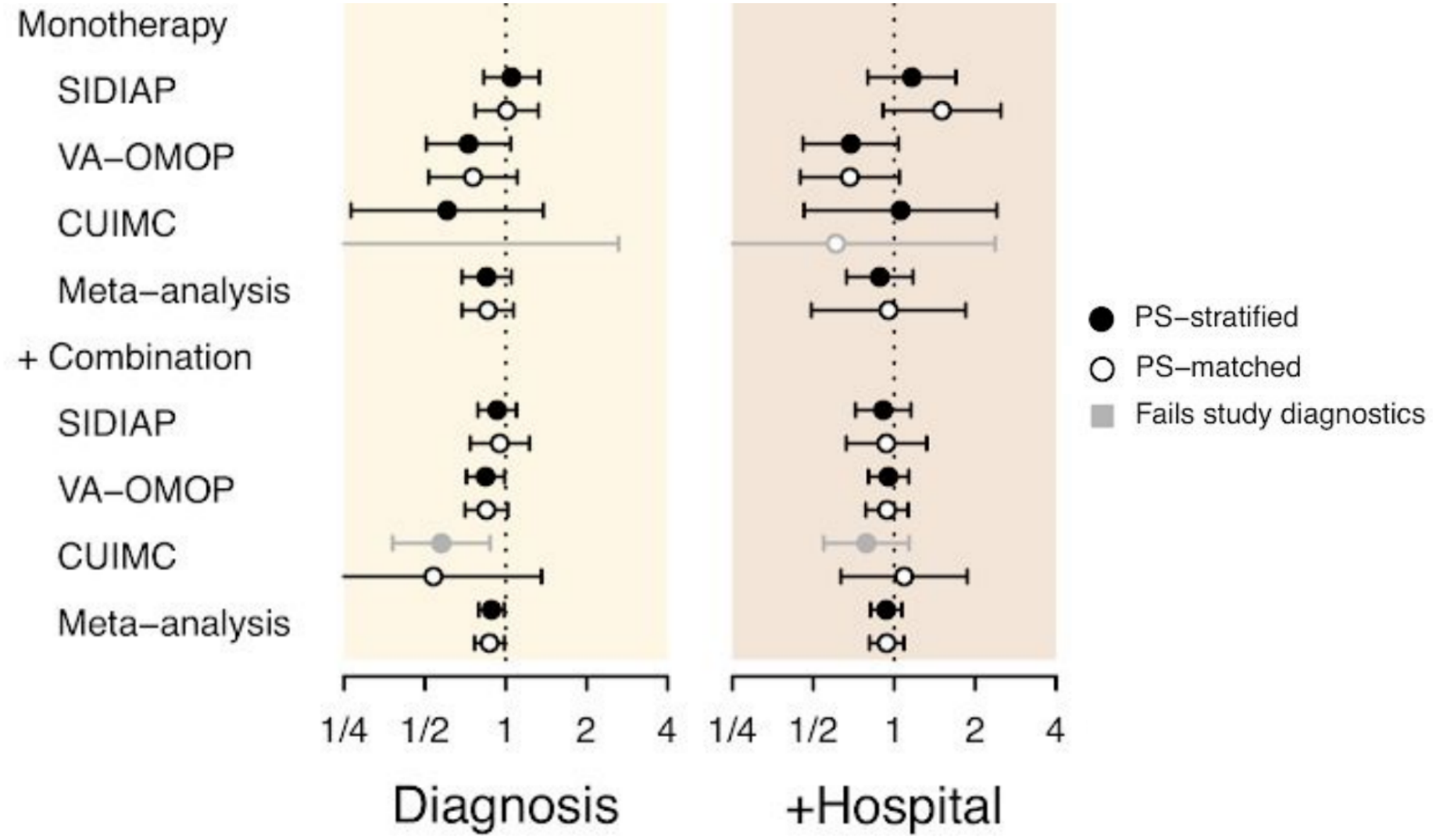


- Baseline differences in diabetes, CKD, heart disease, heart failure, AF
- PS-methods capably balanced baseline covariates, except for PS-stratification in the CUIMC cohort

Calibrated HRs: ACE/ARB vs. CCB/THZ



Calibrated HRs: ACE vs. ARB



Key Limitations

- Defining drug exposure using “prevalent” not “new” use
  - We may adjust for mediators on the causal pathway between exposure and outcome
  - COVID-19 unlikely to have affected decision to initiate one drug versus another
  - Depletion of susceptible is likely minimal
  - Biological mechanisms relating to ACE2 expression may require chronic exposure

- Defining COVID-19 using diagnostic codes and positive test results underestimates the number of true cases
  - May vary by data partner, depending on local-area testing strategies
  - Analyses of COVID-19 hospitalization outcome produced concordant results

Conclusions

- These findings support regulatory and clinical society guidance not to modify ACE/ARB treatment on the basis of COVID-19 risk

- Marginal differences observed between ACEs and ARBs do not warrant class switching to reduce COVID-19 susceptibility

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Links to additional documentation

- Open-source OHDSI CohortMethod R package:
  - https://ohdsi.github.io/CohortMethod/
- Pre-specified ICARIUS protocol and start-to-finish open and executable source code
  - https://github.com/ohdsi-studies/Covid19Icarius
- Interactive web application presenting study diagnostics and results for all study effects
  - https://data.ohdsi.org/IcariusSusceptibility
- Pre-print manuscript, publicly posted to MedRxiv:
  - https://www.medrxiv.org/content/10.1101/2020.06.11.20125849v1