Title

Comparative safety and effectiveness of angiotensin converting enzyme inhibitors and thiazides and thiazide-like diuretics under strict monotherapy.

Journal

The Journal of Clinical Hypertension, 26(4)

Authors

Anand, Tara
Bu, Fan
Schuemie, Martijn
et al.

Publication Date

2024-04-01

DOI

10.1111/jch.14793

Peer reviewed

Received: 27 December 2023 | Revised: 12 February 2024 | Accepted: 15 February 2024

DOI: 10.1111/jch.14793

SHORT RESEARCH ARTICLE

WILEY

Comparative safety and effectiveness of angiotensin converting enzyme inhibitors and thiazides and thiazide-like diuretics under strict monotherapy

Tara V. Anand MA, MPhil[1] | Fan Bu PhD[2,3] | Martijn J. Schuemie PhD[2,4] | Marc A. Suchard MD, PhD[2,5,6] | George Hripcsak MD, MS[1]

[1]Department of Biomedical Informatics, Columbia University Medical Center, New York, New York, USA

[2]Department of Biostatistics, Fielding School of Public Health, University of California, Los Angeles, California, USA

[3]Department of Biostatistics, University of Michigan, Ann Arbor, Michigan, USA

[4]Global Epidemiology, Johnson & Johnson, Titusville, New Jersey, USA

[5]Department of Human Genetics, David Geffen School of Medicine at UCLA, University of California, Los Angeles, California, USA

[6]VA Informatics and Computing Infrastructure, US Department of Veterans Affairs, Salt Lake City, Utah, USA

Correspondence
George Hripcsak, Department of Biomedical Informatics, Columbia University Medical Center, New York, NY, USA.
Email: hripcsak@columbia.edu

Funding information
National Institutes of Health, Grant/Award Numbers: R01 HL169954, R01 LM006910, T15 LM007079

Abstract

Previous work comparing safety and effectiveness outcomes for new initiators of angiotensin converting-enzyme inhibitors (ACEi) and thiazides demonstrated more favorable outcomes for thiazides, although cohort definitions allowed for addition of a second antihypertensive medication after a week of monotherapy. Here, we modify the monotherapy definition, imposing exit from cohorts upon addition of another antihypertensive medication. We determine hazard ratios (HR) for 55 safety and effectiveness outcomes over six databases and compare results to earlier findings. We find, for all primary outcomes, statistically significant differences in effectiveness between ACEi and thiazides were not replicated (HRs: 1.11, 1.06, 1.12 for acute myocardial infarction, hospitalization with heart failure and stroke, respectively). While statistical significance is similarly lost for several safety outcomes, the safety profile of thiazides remains more favorable. Our results indicate a less striking difference in effectiveness of thiazides compared to ACEi and reflect some sensitivity to the monotherapy cohort definition modification.

KEYWORDS
angiotensin-converting enzyme inhibitor, anti-hypertensive therapy, comparative effectiveness, diuretic, hypertension, monotherapy, thiazide

1 | BACKGROUND

Current guidance for specific first-line antihypertensive medication is limited, based largely on expert opinion due to lacking clinical trials comparing various medications and drug classes.[1] Previously, Suchard et al.[2] generated hazard ratios (HR) comparing risks for new initiators of different drug classes for various safety and effectiveness outcomes with evidence demonstrating better primary effectiveness and safety for the class of thiazides and thiazide-like diuretics, referred to as "thiazides" throughout, compared to angiotensin converting-enzyme inhibitors (ACEi).

This comparison left open the possibility for one initiator group to more frequently have a second antihypertensive medication added after one week of monotherapy, potentially biasing results. We therefore adjusted the definition for monotherapy cohorts to impose exit from the cohort upon the start of any additional antihypertensive

medication. We calculated hazard ratios for 55 safety and effectiveness outcomes comparing cohorts on monotherapy thiazides and ACEi across six databases. We compared our findings to those of Suchard et al.[2] to assess the impact of the modified monotherapy cohort definitions on effect sizes and evaluation of thiazides compared to ACEi for first-line hypertension treatment.

2 | METHODS

A retrospective new-user cohort design[3,4] was used to estimate propensity-score[5] adjusted hazard ratios for three primary, six secondary and 46 safety outcomes comparing monotherapy drug classes of thiazides and ACEi. The primary effectiveness outcomes are acute myocardial infarction (AMI), hospitalization for heart failure (HF), and stroke. The secondary effectiveness outcomes are cardiovascular-related mortality, ischemic stroke, hemorrhagic stroke, heart failure, sudden cardiac death, and chest pain or angina. The safety outcomes include hypertension medication side effects and can be noted in the study protocol.[a]

Criteria for inclusion in monotherapy treatment cohorts of either thiazides or ACEi were defined to include patients initiating a single hypertension treatment from either class, with the index date as the day treatment starts for the first time in the person's history. For each outcome, patients with an event prior to treatment initiation are excluded. Exit is imposed from the cohort upon start of an additional hypertension treatment. Patient time at risk is defined as on-treatment, following patients from the index date until treatment or their record ends. Cohorts and the study package were created in ATLAS,[6] based on cohort definitions from the protocol and software from Suchard et al. when available.

Large-scale propensity score[2,5,7] models were created for each database using regularized regression over a large set of baseline patient characteristics. Hazard ratios were determined by Cox proportional hazard models and propensity-score stratification, which were assessed for balance and equipoise.[8]

The study was conducted using the open-source Observational Health Data Science and Informatics (OHDSI) CohortMethod R package. Further details on cohort definitions, code and data summary are available at: https://github.com/ohdsi-studies/LegendHtnTrueMonotherapy.

Analyses were performed across six observational databases including four administrative claims and two electronic health record (EHR) databases, earlier versions of which were analyzed in Suchard et al.[2] All databases are part of the OHDSI distributed data network[6] and standardized to OHDSI's Observational Medical Outcomes Partnership common data model. The claims databases are: IBM MarketScan Commercial Claims and Encounters (CCAE), Optum's de-identified Clinformatics® Data Mart Database (Optum Clinformatics), IBM MarketScan Medicare Supplemental Beneficiaries (MDCR), and IBM MarketScan Multistate Medicaid (MDCD). The EHR databases are: Optum® de-identified Electronic Health Record dataset (Optum EHR), and Columbia University Irving Medical Center (CUIMC). All data partners had prior Institutional Review Board approval or exemption for their participation.

[a] https://github.com/ohdsi-studies/LegendHtnTrueMonotherapy/blob/main/documents

3 | RESULTS

Across all databases, longitudinal data from 4 601 675 patients with a first exposure to either thiazides or ACEi, and at least 365 days of prior observation, were available. Of these patients, 61.1% initiated ACEi. CCAE and Optum EHR contributed the most records at 37.3% and 33.7%, respectively.

Calculated HRs under the modified study design were compared to those of the original study.[2] We performed one meta-analysis over results from the six databases included in our analysis, and one over the results from earlier versions of these databases included in the 2019 study.[2] The magnitudes of the HRs and confidence intervals (CI) for the meta-analyses of the original and modified study designs for all outcomes can be found in Figure 1 and Table 1.

The differences between the HRs of the meta-analyses for the modified monotherapy and original study designs were not statistically significant at a 5% level for all but one of 55 outcomes, acute renal failure (safety outcome; $p = .02$). For this outcome, while the original study showed a significant increase in risk for patients on ACEi compared to thiazides (HR = 1.34 [95% CI: 1.12–1.59]), our analyses failed to show a significant difference (HR = 1.03 [95% CI: 0.89–1.19]), which more closely aligns with prior knowledge of associated outcomes. For the safety outcomes of cough (HR = 1.35 [95 % CI: 1.20–1.53]) and angioedema (HR = 2.98 [95% CI: 2.29–3.87]), known side effects of ACEi, hypokalemia (HR = 0.36 [95% CI: 0.2780–0.47]), a known side effect of thiazides, and hyperkalemia (HR = 1.72 [95% CI: 1.47–2.00]) known to show an inverse relationship of hypokalemia, the HRs of the two study designs either remained consistent or showed a stronger relationship and greater alignment with prior knowledge in the modified study compared to the original. Such consistencies lend credibility to the findings of the modified study design.

For all three primary outcomes, the HR moved considerably towards the null and failed to show significant differences for ACEi compared to thiazides (AMI: HR = 1.11 [95% CI: 0.97–1.27]; hospitalization with HF: HR = 1.06 [95% CI: 0.91–1.22]; stroke: HR = 1.12 [95% CI: 1.00–1.23]), despite the 2019 study demonstrating a statistically significant difference for all three primary outcomes (AMI: HR = 1.22 [95% CI: 1.05–1.39]; hospitalization with HF: HR = 1.21 [95% CI: 1.04–1.40]; stroke: HR = 1.22 [95% CI: 1.05–1.41]). Note that the differences between the HR of the two study designs for AMI, hospitalization with HF, and stroke, were not statistically different from each other (p-values: .36, .16, .36, respectively).

Our study showed a significantly lower risk for thiazides for only two secondary effectiveness outcomes: cardiovascular-related mortality and hemorrhagic stroke. For nine of the safety outcomes that showed a statistically significant difference in risk under the original study design, the modified study failed to replicate significance. Under

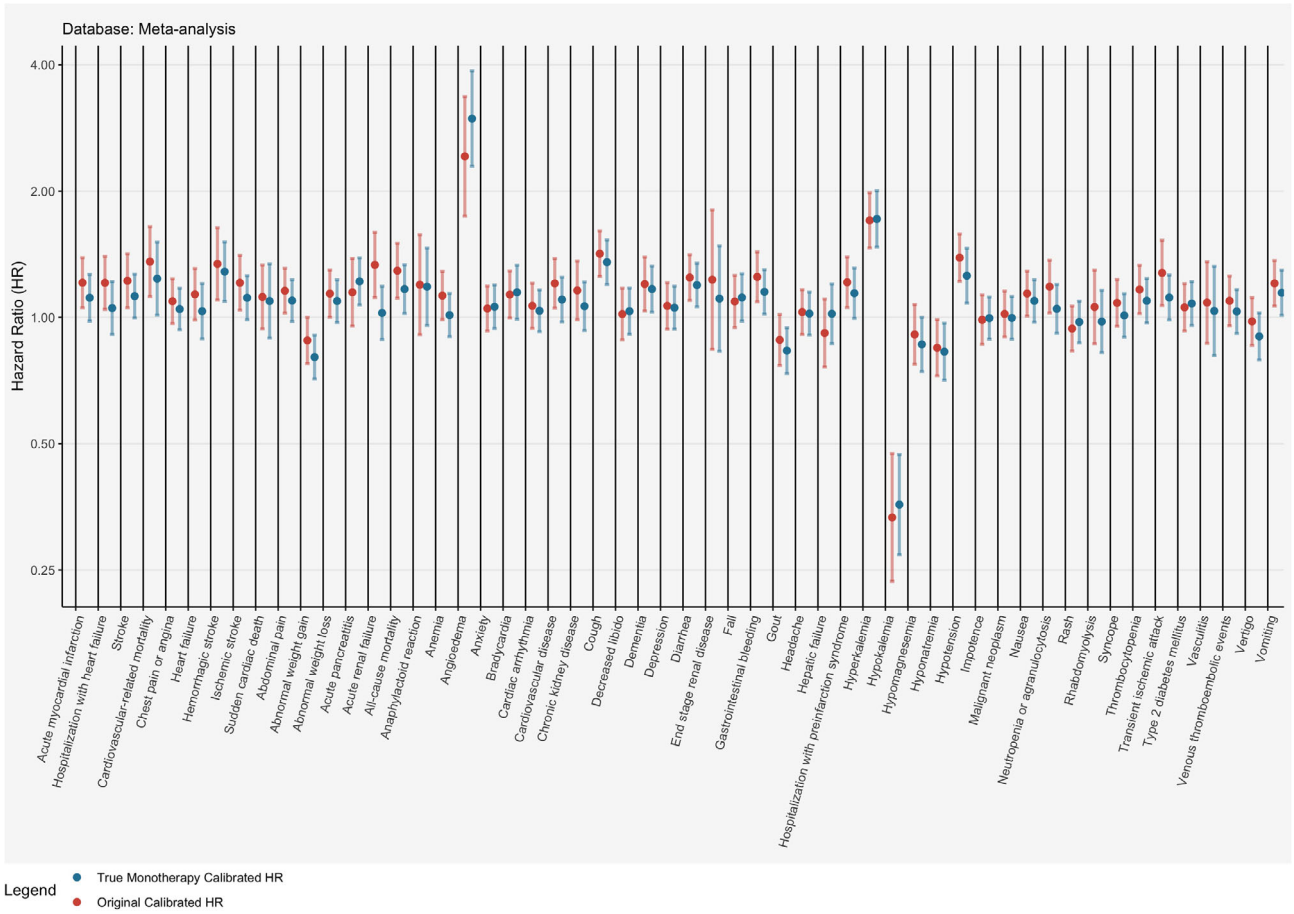

FIGURE 1 Magnitudes and confidence intervals for log hazard ratios for meta-analyses over six databases from the 2019 (Original) and current (True monotherapy) study for all outcomes.

our analysis, thiazides showed a statistically significant benefit for 10 safety outcomes, compared to ACEi which demonstrated such benefit for four safety outcomes.

To evaluate whether changes in HRs were due to shortened times-at-risk, we compared days-at-risk for each outcome included in the present and 2019[2] studies and found similarity in values. For AMI, for example, the summary median days-at-risks over all databases for the target and comparator populations were 534 (IQR: 215–2624) and 490 (IQR: 181—2403) respectively in the present study compared to 656 (IQR: 275–3462) and 694 (IQR: 258–3536) in the 2019 study.[2]

4 | DISCUSSION

The new monotherapy definition resulted in estimates for the three primary outcomes that, while lacking significantly shifted confidence intervals relative to the first study's[2] results, were no longer statistically significant. Two secondary outcomes, cardiovascular-related mortality and hemorrhagic stroke, were consistent, favoring thiazides. While there may still be small differences in effectiveness between ACEi and thiazides, our adjusted monotherapy cohort definitions result in evidence failing to show a striking distinction. Nevertheless, the safety profile still favors thiazides over ACEi, with thiazides demonstrating a significantly lower risk for a greater number of safety outcomes, compared to ACEi namely, acute pancreatitis, all-cause mortality, angioedema, cough, dementia, diarrhea, gastrointestinal bleeding, hyperkalemia, hypotension, and vomiting.

Generally, our results show some consistency with those of Suchard et al.[2]; the HRs calculated under our modified study design do not differ substantially from those determined in the original study for all but one outcome. However, the difference in statistically significant results do suggest some sensitivity to the cohort definition modification.

Still, where little differences between classes of other antihypertensive medications for safety and effectiveness outcomes were previously observed,[2] the significantly reduced risk for several safety outcomes for thiazides compared to ACEi are noteworthy. More than 40 million people take ACEi[9] and the implication for reduction of side effects and improved safety for changing prescribing patterns is consequential. While we recognize dual therapy is more common, knowing the effect of individual drugs is still informative.

One limitation of the study is that it was executed on different versions of the databases due to the passage of time since the original study. We do not expect major changes in drug outcomes and side effects over the past three years.

TABLE 1 Magnitudes, lower and upper 95% confidence interval (CI) bounds, and *p*-values for hazard ratios for meta-analyses over six databases from the 2019 study and current (True monotherapy) study for all outcomes.

		2019 Study				Current true monotherapy study			
Outcome	**Outcome type**	***p*-value**	**HR**	**CI Lower**	**CI Upper**	***p*-value**	**HR**	**CI Lower**	**CI Upper**
Acute myocardial infarction	Primary effectiveness	**.01**	**1.21**	**1.05**	**1.39**	.10	1.11	0.98	1.27
Hospitalization with heart failure	Primary effectiveness	**.01**	**1.21**	**1.04**	**1.40**	.49	1.05	0.91	1.22
Stroke	Primary effectiveness	**.01**	**1.22**	**1.05**	**1.42**	.06	1.12	1.00	1.27
Cardiovascular-related mortality	Secondary effectiveness	**.00**	**1.36**	**1.12**	**1.65**	**.04**	**1.24**	**1.01**	**1.51**
Chest pain or angina	Secondary effectiveness	.16	1.09	0.97	1.24	.43	1.05	0.93	1.17
Heart failure	Secondary effectiveness	.08	1.13	0.99	1.31	.66	1.03	0.89	1.20
Hemorrhagic stroke	Secondary effectiveness	**.00**	**1.34**	**1.10**	**1.64**	**.00**	**1.29**	**1.09**	**1.51**
Ischemic stroke	Secondary effectiveness	**.01**	**1.21**	**1.04**	**1.41**	.08	1.11	0.99	1.26
Sudden cardiac death	Secondary effectiveness	.21	1.12	0.94	1.33	.39	1.09	0.89	1.34
Abdominal pain	Safety	**.02**	**1.16**	**1.02**	**1.31**	.12	1.10	0.98	1.23
Abnormal weight gain	Safety	.05	0.88	0.78	1.00	**.00**	**0.80**	**0.71**	**0.91**
Abnormal weight loss	Safety	**.05**	**1.14**	**1.00**	**1.30**	.13	1.09	0.97	1.23
Acute pancreatitis	Safety	.15	1.15	0.95	1.38	**.00**	**1.22**	**1.07**	**1.39**
Acute renal failure	Safety	**.00**	**1.33**	**1.12**	**1.59**	.74	1.02	0.89	1.19
All-cause mortality	Safety	**.00**	**1.29**	**1.11**	**1.50**	**.02**	**1.17**	**1.02**	**1.34**
Anaphylactoid reaction	Safety	.20	1.20	0.91	1.57	.12	1.18	0.96	1.46
Anemia	Safety	.08	1.13	0.99	1.29	.83	1.01	0.90	1.14
Angioedema	Safety	**.00**	**2.42**	**1.74**	**3.36**	**.00**	**2.98**	**2.29**	**3.87**
Abnormal weight gain	Safety	.05	0.88	0.78	1.00	**.00**	**0.80**	**0.71**	**0.91**
Anxiety	Safety	.44	1.05	0.93	1.19	.34	1.06	0.94	1.19
Bradycardia	Safety	.06	1.13	1.00	1.29	.07	1.15	0.99	1.33
Cardiac arrhythmia	Safety	.31	1.07	0.94	1.21	.54	1.04	0.92	1.16
Cardiovascular disease	Safety	**.01**	**1.21**	**1.05**	**1.38**	.12	1.10	0.98	1.25
Chronic kidney disease	Safety	.07	1.16	0.99	1.36	.37	1.06	0.93	1.21
Cough	Safety	**.00**	**1.42**	**1.25**	**1.61**	**.00**	**1.35**	**1.20**	**1.53**
Decreased libido	Safety	.80	1.02	0.88	1.17	.60	1.03	0.91	1.17
Dementia	Safety	.01	1.20	1.04	1.39	**.02**	**1.17**	**1.03**	**1.33**
Depression	Safety	.33	1.07	0.94	1.21	.37	1.05	0.94	1.19
Diarrhea	Safety	**.00**	**1.24**	**1.10**	**1.41**	**.00**	**1.19**	**1.06**	**1.35**
End stage renal disease	Safety	.29	1.23	0.84	1.80	.49	1.11	0.83	1.48
Fall	Safety	.23	1.09	0.95	1.26	.10	1.12	0.98	1.27
Gastrointestinal bleeding	Safety	**.00**	**1.25**	**1.09**	**1.43**	**.02**	**1.15**	**1.02**	**1.30**
Gout	Safety	.08	0.88	0.77	1.02	**.00**	**0.83**	**0.74**	**0.94**
Headache	Safety	.64	1.03	0.91	1.16	.73	1.02	0.91	1.15
		2019 study				*Current true monotherapy study*			
Outcome	***Outcome type***	***p-value***	***HR***	***CI Lower***	***CI Upper***	***p-value***	***HR***	***CI Lower***	***CI Upper***
Hepatic failure	Safety	.37	0.92	0.76	1.11	.81	1.02	0.87	1.20
Hospitalization with preinfarction syndrome	Safety	**.01**	**1.21**	**1.06**	**1.39**	.06	1.14	0.99	1.31
Hyperkalemia	Safety	**.00**	**1.70**	**1.46**	**1.98**	**.00**	**1.72**	**1.47**	**2.00**
Hypokalemia	Safety	**.00**	**0.33**	**0.23**	**0.47**	**.00**	**0.36**	**0.27**	**0.47**
Hypomagnesemia	Safety	.26	0.91	0.77	1.07	.05	0.86	0.74	1.00
Hyponatremia	Safety	**.03**	**0.85**	**0.73**	**0.99**	**.02**	**0.83**	**0.71**	**0.97**

(Continues)

TABLE 1 (Continued)

		2019 study				Current true monotherapy study			
Outcome	*Outcome type*	*p-value*	*HR*	*CI Lower*	*CI Upper*	*p-value*	*HR*	*CI Lower*	*CI Upper*
Hypotension	Safety	**.00**	**1.39**	**1.22**	**1.58**	**.00**	**1.26**	**1.08**	**1.46**
Impotence	Safety	.85	0.99	0.86	1.13	.91	1.00	0.89	1.12
Malignant neoplasm	Safety	.77	1.02	0.90	1.16	.92	1.00	0.89	1.12
Nausea	Safety	**.04**	**1.14**	**1.01**	**1.29**	.13	1.09	0.97	1.23
Neutropenia or agranulocytosis	Safety	**.02**	**1.18**	**1.02**	**1.37**	.49	1.05	0.92	1.20
Rash	Safety	.33	0.94	0.83	1.06	.66	0.98	0.87	1.09
Rhabdomyolysis	Safety	.58	1.06	0.87	1.30	.79	0.98	0.82	1.16
Syncope	Safety	.23	1.08	0.95	1.23	.86	1.01	0.90	1.14
Thrombocytopenia	Safety	**.02**	**1.17**	**1.02**	**1.33**	.14	1.10	0.97	1.24
Transient ischemic attack	Safety	**.01**	**1.28**	**1.07**	**1.53**	.08	1.12	0.99	1.26
Type 2 diabetes mellitus	Safety	.40	1.06	0.93	1.20	.21	1.08	0.96	1.22
Vasculitis	Safety	.48	1.08	0.87	1.36	.78	1.04	0.81	1.32
Venous thromboembolic events	Safety	.19	1.10	0.96	1.26	.60	1.03	0.92	1.17
Vertigo	Safety	.74	0.98	0.86	1.12	.11	0.90	0.79	1.02
Vomiting	Safety	**.00**	**1.21**	**1.06**	**1.37**	**.03**	**1.14**	**1.01**	**1.29**

Statistically significant results are in bold.

5 | CONCLUSIONS

In this study, hazard ratios were determined for 55 outcomes to compare the safety and effectiveness of ACEi and thiazides with a modified cohort definition for monotherapy treatment and results are compared to Suchard et al.[2] Statistically significant differences in effectiveness between ACEi and thiazides were not replicated for all three primary outcomes, although the shift in confidence intervals relative to Suchard et al.[2] was not significant. Despite several safety outcomes similarly lacking statistically significant differences in our analysis, the safety profile of thiazides compared to ACEi still remained more favorable. Overall, our results indicate a less striking difference particularly with regards to effectiveness of thiazides compared to ACEi and our findings reflect some sensitivity to the monotherapy cohort definition modification.

AUTHOR CONTRIBUTIONS

Tara V. Anand: Conceptualization; Methodology; Software; Validation; Formal analysis; Investigation; Data Curation; Writing—Original Draft; Visualization; Project administration. **Fan Bu**: Methodology; Software; Validation; Formal analysis; Investigation; Data curation; Writing—Review & Editing. **Martijn J. Schuemie**: Conceptualization; Methodology; Software; Validation; Formal analysis; Resources; Data Curation; Writing—Review & Editing; Supervision. **Marc A. Suchard**: Conceptualization; Methodology; Software; Validation; Formal analysis; Resources; Data Curation; Writing—Review & Editing; Supervision; Project administration; Funding acquisition. **George Hripcsak**: Conceptualization; Methodology; Validation; Formal analysis; Resources; Data Curation; Writing—Review & Editing; Visualization; Supervision; Project administration; Funding acquisition.

ACKNOWLEDGMENTS

This work is partially supported through US National Institutes of Health grants (T15 LM007079, R01 LM006910, and R01 HL169954).

CONFLICT OF INTEREST STATEMENT

M.J.S. is an employee of Johnson & Johnson. M.A.S. has received grant funding from Janssen Research & Development, a subsidiary of Johnson & Johnson to support methods research not directly related to this study. Johnson & Johnson and Janssen did not have input in the design, execution, interpretation of results or decision to publish. All other authors declare no competing interests.

DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared publicly due to privacy of patient health information.

ORCID

Tara V. Anand MA, MPhil https://orcid.org/0000-0002-2551-867X

REFERENCES

1. Hripcsak G, Schuemie MJ, Madigan D. Drawing reproducible conclusions from observational clinical data with OHDSI. *Yearb Med Inform*. 2021;30(1):283-289.
2. Suchard MA, Schuemie MJ, Krumholz HM, et al. Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes. *Lancet*. 2019;394(10211):1816-1826.

3. Ryan PB, Schuemie MJ, Gruber S, et al. Empirical performance of a new user cohort method: lessons for developing a risk identification and analysis system. *Drug Saf*. 2013;36(1):S59-S72. Suppl.
4. Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. *Am J Epidemiol*. 2016;183(8): 758-764.
5. Tian Y, Schuemie MJ, Suchard MA. Evaluating large-scale propensity score performance through real-world and synthetic data experiments. *Int J Epidemiol*. 2018;47(6):2005-2014.
6. Hripcsak G, Duke JD, Shah NH, et al. Observational health data sciences and informatics (OHDSI): opportunities for observational researchers. *Stud Health Technol Inform*. 2015;216:574-578.
7. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983; 70(1):41.
8. Walker AM, Patrick AR, Lauer MS, et al. A tool for assessing the feasibility of comparative effectiveness research. *Comp Effect Res*. 2013;3:11-20.
9. Messerli FH, Nussberger J. Vasopeptidase inhibition and angio-oedema. *Lancet*. 2000;356(9230):608-660.

How to cite this article: Anand TV, Bu F, Schuemie MJ, Suchard MA, Hripcsak G. Comparative safety and effectiveness of angiotensin converting enzyme inhibitors and thiazides and thiazide-like diuretics under strict monotherapy. *J Clin Hypertens*. 2024;26:425–430.
https://doi.org/10.1111/jch.14793