Efficacy and Safety of Sacubitril/Valsartan in Adverse Cardiovascular Event Reduction and Hypertension Control Among Asians: A Systematic Review and Meta-analysis of Randomized Controlled Trials

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Declaration of conflicts of interest: None.

Abstract

BACKGROUND: Sacubitril/valsartan is currently a standard medication in the treatment of reduced ejection fraction heart failure (HFrEF), and studies have also shown its efficacy for controlling hypertension. However, its efficacy varies between populations, and current recommendations are predominantly based on non-Asian data. Hence, this study synthesizes the available evidence to determine its overall efficacy and safety among Asians.

METHODS: A systematic search through PubMed, ScienceDirect, Cochrane, HERDIN PLUS, and ClinicalTrials.gov was done to include randomized controlled trials with Asian data comparing sacubitril/valsartan against an active control. The Cochrane Risk of Bias 2.0 was used to assess each article for bias. Forest plots in fixed-effects model for major adverse cardiovascular events (MACEs), hypertension control, and safety were created using RevMan 5.4.

RESULTS AND DISCUSSION: Ten articles with an overall low risk of bias were included involving 6120 Asians. Sacubitril/valsartan showed better hypertension control against conventional angiotensin blocker (odds ratio [OR], 1.63; confidence interval [CI], 1.38–1.92; I^2 = 7%). However, MACE reduction was not significant in HFrEF (hazard ratio, 0.89; CI, 0.73–1.08; I^2 = 0%) or acute myocardial infarction (hazard ratio, 0.90; CI, 0.65–1.24; I^2 = 0%). Safety was comparable to conventional angiotensin-converting enzyme inhibitors/angiotensin receptor blocker (ARB) with a severe adverse event OR of 0.81 (CI, 0.44–1.50; I^2 = 38%) and nonsevere adverse event OR of 1.09 (CI, 0.88–1.35; I^2 = 44%). These results implicate the need for efficacy studies focused on Asians, reassessment of the strength of recommendations in the treatment of heart failure, and consideration of sacubitril/valsartan as a treatment option for hypertension.

CONCLUSION: Among Asians, better hypertension control is seen with LCZ696 than conventional ARB. However, MACE reduction in HFrEF or acute myocardial infarction is insignificant, although there is a trend toward benefit. Finally, safety is comparable to conventional angiotensin-converting enzyme inhibitors/ARBs.\.

KEYWORDS: acute myocardial infarction, Asians, heart failure, hypertension, LCZ696, sacubitril/valsartan

BACKGROUND

Cardiovascular disease remains to be the leading cause of death in both developed and developing countries.[1–3] In the United States, heart disease caused 20% of the total deaths in 2020.[2] Likewise, the Philippine Statistics Authority reported ischemic heart disease as the top cause of mortality in 2020 and the first half of 2021 despite the COVID-19 pandemic.[3] These problems fuel the continuous search for better treatment options to significantly reduce mortality and control cardiovascular risk factors across varying populations. With these in mind, ethnicity continues to be an important factor to consider in treating cardiovascular disease. In 2020, non-Hispanic Asians experienced a disproportionate rise in deaths caused by heart disease in the United States (risk ratio [RR], 1.15; 95% confidence interval [CI], 1.09–1.21; $P < 0.001$).[4] Concurrently, hypertension, which remains to be the most common, readily identifiable, and reversible risk factor for cardiovascular disease, was found to be significantly more prevalent among Southeast Asians (odds ratio [OR], 2.0; 95% CI, 1.2–3.4).[5]

Sacubitril/valsartan, which consists of the neprilysin inhibitor sacubitril and the angiotensin receptor blocker (ARB) valsartan, was designed to maximize the beneficial effects of both medications and minimize the risk of serious angioedema.[6–10] The PARADIGM-HF was the largest international trial examining the efficacy of sacubitril/valsartan, which showed superiority over enalapril in reducing the risk for adverse cardiovascular events (hazard ratio [HR], 0.80; 95% CI, 0.73–0.87; $P < 0.001$).[11] Since the trial's publication, sacubitril/valsartan has gained worldwide recognition as one of the pillars of medical management for heart failure with reduced ejection fraction gaining a class I recommendation from European and American guidelines. Furthermore, besides reducing adverse cardiovascular events, several studies have also evaluated its efficacy in controlling hypertension with promising results.[12–23]

However, the efficacy of sacubitril/valsartan seems to vary between populations. In the PARADIGM-HF, only the White subgroup showed a statistically significant benefit, unlike for Asians, Blacks, and Native Americans.[24] Smaller studies also report varying results of its efficacy.[25,26] Furthermore, the incidences of adverse events in Asians treated with sacubitril/valsartan reported in individual clinical trials are still controversial.[18,24,25,27–30] Hence, to clarify the disparity of reported data, this study aims to synthesize the available evidence to determine the overall efficacy and safety of sacubitril/valsartan among Asians.

METHODS

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guideline in reporting data was used.[31] Eligibility criteria were formed using the PICOM framework.[32] Data extraction followed the Cochrane recommendations for data collection.[33]

Eligibility Criteria

An article was considered eligible for inclusion if it enrolled Asians 18 years or older to both treatment and control arms, compared with sacubitril/valsartan 400 mg/d against an active medication such as an ARB or an angiotensin-converting enzyme inhibitor (ACEi) in terms of (*a*) MACEs defined as a composite of cardiovascular mortality and heart failure hospitalization, myocardial infarction, and stroke; (*b*) blood pressure control defined as achieving a mean sitting systolic blood pressure of less than 140 mm Hg and a diastolic blood pressure of less than 90 mm Hg, and (*c*) safety including SAEs and nonserious adverse events during the treatment period. Only RCTs were included for analysis.

Exclusion Criteria

An article was excluded if it did not report effect measures on any of the desired outcomes.

Information Sources

The search used topic-based strategies designed for each database and registry from inception to June 2023. There were no language or geographic restrictions. Article search was limited to systematic reviews, meta-analyses, and RCTs. Manual "snowball" search from the reference lists of included articles was done to identify additional studies. Search for unpublished articles was also done through clinical trial registries (ie, Clinicaltrials.gov, HERDIN PLUS) and databases (ie, PubMed, ScienceDirect, Cochrane)

Search Strategies

The following keywords and corresponding MeSH terms were used for the systematic search from the information sources: "Sacubitril/valsartan" or "LCZ696" AND "Asians" or "Mortality" or "Heart Failure Hospitalization" or "Hypertension" or "Adverse events."

Study Records

Selection Process

Two researchers (P.V.C.) and (W.A.) independently performed database and registry search and reviewed the titles and abstracts to identify articles for applicability assessment. In case of disagreement, a third researcher (J.B.C.) was consulted to make a final decision.

Data Management

Articles for applicability assessment were stored into a computer document folder, and data collected were encoded into an Excel file (Microsoft Corp, Redmond, Washington).

Applicability Assessment

An article was determined to be applicable if it included Asians treated with sacubitril/valsartan (LCZ696) and reported effect measures for the desired outcomes such as MACEs (composite of cardiovascular mortality, heart failure hospitalization, myocardial infarction), blood pressure control, and adverse events in a RCT.

Data Collection Process

The data extraction form was based on the recommendations from Chapter 5 of the Cochrane Handbook for Systematic

Reviews.[33] Extracted data were compared, and discrepancies were resolved through discussion.

Data Items
Eligible outcomes were as follows:

- Major adverse cardiovascular events defined as a composite of cardiovascular death and heart failure hospitalization, stroke, and myocardial infarction.
- Blood pressure control defined as achieving a mean sitting systolic blood pressure of less than 140 mm Hg and a diastolic blood pressure of less than 90 mm Hg.
- Safety is defined as the reduction of (1) SAEs, which include adverse events that result in death, require either inpatient hospitalization or the prolongation of hospitalization, are life-threatening, or result in a persistent or significant disability/incapacity; and of (2) nonserious adverse events including cough, hypotension, elevated creatinine, hyperkalemia, upper respiratory tract infection, and dizziness.

We also collected participant information such as ethnicity and country of origin, study methods such as overall design, sampling mechanism, treatment assignment, and length of follow-up, as well as funding, intervention dose, and timing.

Assessing for Bias and Reporting
The Cochrane Risk of Bias 2.0 (RoB-2) tool was used to assess for bias of the selected articles. The RoB-2 addresses five specific domains: (1) bias arising from the randomization process, (2) bias due to deviation from intended interventions, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, and (5) bias in selection of the reported result.[34] Two review authors independently applied the tool to each included study. Any discrepancies in judgments of risk of bias or justifications for judgments were resolved by discussion to reach consensus between the two review authors, with a third review author acting as an arbiter if necessary. Following guidance given for RoB-2, we derived an overall summary "Risk of Bias" judgment (low, some concerns, high) for each specific outcome, whereby the overall risk of bias for each study was determined by the highest RoB level in any of the domains that were assessed. The RoBVis (Risk of Bias Visualization) tool was used to present the risk-of-bias assessments of each article.[35]

To assess for significant publication bias, the Comprehensive Meta-Analysis Software was used to create funnel plots for each synthesis, and asymmetry was analyzed using Begg and Mazumdar's[36] rank correlation and Egger's regression intercept.[37] The PRISMA 2020 checklist was used as guide to avoid reporting bias in this study.[31]

Effect Measures and Synthesis Methods
Data from each included study were tabulated into an Excel (Microsoft Corp) file for comparison. For both published and unpublished articles, the reported HRs for MACEs were obtained from each study. WebPlotDigitizer 4.4 was used for extracting the numerical adjusted HR from the study by McMurray et al,[24] which presented the data only in graphical format. The reported adjusted ORs for blood pressure control were obtained from three studies and used to create a forest plot. Finally, safety was determined by calculating the OR for occurrence of adverse events between sacubitril/valsartan and control. The ORs for the most common adverse events such as hypotension, hyperkalemia, dizziness, cough, elevated creatinine >5.5mmol/L, and upper respiratory tract infection were also determined. RevMan 5.4 was used to create the forest plots in a Mantel-Haenszel fixed-effects model at 95% CI. Heterogeneity was assessed by using the I^2 test and Cochran's χ^2 test. The total variation in the studies was described by the I^2 statistic, which reflected heterogeneity. An $I^2 \geq 50\%$ or a corresponding $P < 0.10$ indicated significant heterogeneity among the different studies.

A predetermined subgroup analysis based on indication for treating with sacubitril/valsartan was done to lessen heterogeneity. For the nonserious adverse events, subgroup analysis was performed for the common adverse events mentioned in literature such as cough, hyperkalemia, hypotension, elevated creatinine, dizziness, and upper respiratory tract infection to determine differences in risk.[24,38]

To assess for the robustness of the synthesized results for the study outcomes, sensitivity analysis was performed by reconstructing the forest plot using data from the articles with an overall low risk of bias.

Certainty Assessment
Two reviewers (P.V.C., W.A.) independently used the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) Working Group system to asses for the certainty of evidence based on the study limitations, consistency of effect, imprecision, indirectness, and publication bias. The certainty of evidence was assessed as high, moderate, low, or very low. The following criteria were considered for upgrading the certainty of evidence based on the recommendations described in Sections 8.5 and 8.7 and Chapters 11 and 12 of the Cochrane Handbook: large effect, dose-response gradient, and plausible confounding effect.[39] The GRADEproGDT software was used to prepare the "Summary of Findings" table. The authors justified all decisions to downgrade or upgrade the certainty of studies using footnotes.

RESULTS

Study Selection
As seen in Figure 1, a total of 2249 records were identified from PubMed (n = 281), ScienceDirect (n = 1322), Cochrane (n = 617), HERDIN PLUS (n = 8), and ClinicalTrials.gov (n = 21). After excluding narratives, editorials, duplicates, and studies where neither the title nor the abstract indicated the parameters for inclusion, 32 articles remained. Thirteen articles were excluded for not meeting the inclusion criteria, six articles were excluded for lack of data for Asians, two retrospective cohort studies were also excluded, and three more studies were excluded for lack of control against sacubitril/valsartan. One article was excluded because it did not compare sacubitril/

valsartan with an active medication. Three articles were then identified after snowball searching. Hence, a total of 10 articles qualified the inclusion and exclusion criteria for further analysis.

Study Characteristics

Table 1 shows the characteristics of the 10 included studies that qualified the eligibility criteria. All studies included were RCTs involving Asian patients from China, India, Japan, Philippines, Singapore, South Korea, Taiwan, and Thailand.[18,24–30,41] Most of the included studies were multicenter trials except for the studies by Wang et al[29] and Zhang et al.[30] Six studies reported on MACEs, three studies reported on blood pressure control, five studies reported SAEs, and seven studies reported on nonserious adverse cardiovascular events.

Six RCTs reported on MACEs. The studies by McMurray et al[24] and Tsutsui et al[28] enrolled patients with reduced ejection fraction; the studies by Pfeffer et al,[40] Wang et al,[29] and Zhang et al[30] enrolled patients with acute myocardial infarction; and the study by Solomon et al[26] enrolled patients with heart failure with preserved ejection fraction. The follow-up to outcome determination of the studies included for the MACE outcome was at least 6 months to a median of 39 months. Four of the six studies were funded by pharmaceutical companies.

Three studies determined blood pressure control using a multicenter, randomized, double-blind, parallel-group study design. These studies enrolled patients with mild to moderate hypertension and compared sacubitril/valsartan with active control. Blood pressure control was defined as achieving a systolic blood pressure of less than 140 mm Hg and a diastolic blood pressure of less than 90 mm Hg in all studies included.

Five RCTs reported rates of SAEs, whereas seven reported nonserious adverse events. All studies compared the 400-mg/d dose of sacubitril/valsartan with a conventional ACEi or ARB. Time to follow-up varied ranging from 8 weeks to a median follow-up of 27 months. Two studies declared no conflict of interest, whereas the other seven were primarily funded by one or more pharmaceutical companies.

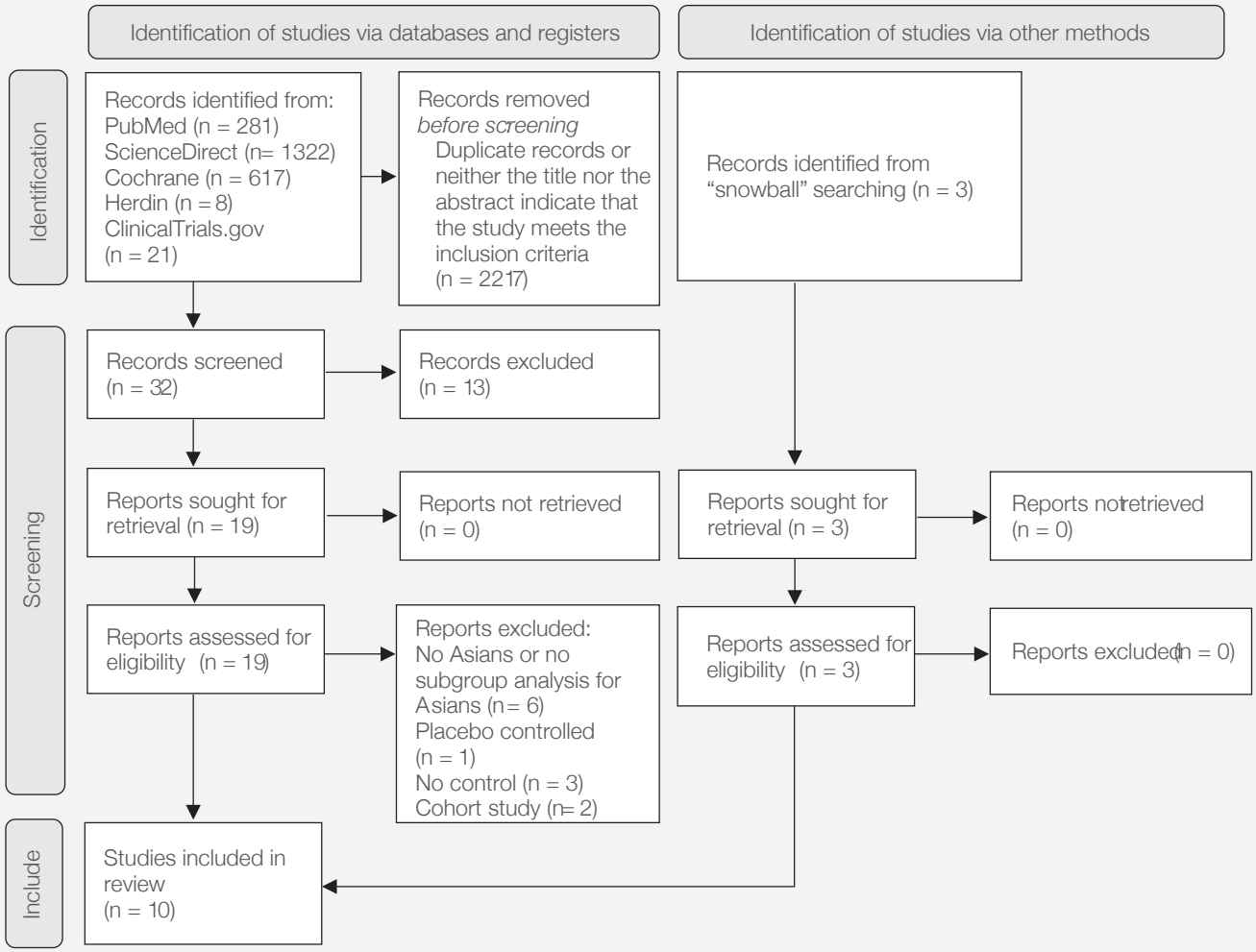


Figure 1. PRISMA 2020 diagram of article selection for systematic review and meta-analysis.
PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1. Characteristics of Included Studies

Study	Design of RCT	Study Population	Treatment Dose (n)	Control (n)	Follow-up	Funding	Outcomes		
							MACEs	BP	Safety
McMurray et al,[24] 2014	Multicenter double-blind,	1509 (18.1%) with HFrEF	200 mg BID (n = 738)	Enalapril 10 mg BID (n = 731)	Median of 27 mo	Novartis Pharma	✓		✓
Supasyndh et al,[18] 2017	Multicenter, double-blind	588 elderly with systolic hypertension	400 mg/d (n = 296)	Olmesartan 20 mg OD (n = 292)	14 wk	Novartis Pharma		✓	✓
Huo et al,[27] 2018	Multicenter, randomized, double-blind	366 with essential hypertension	200 mg and 400 mg/d (n = 478)	Olmesartan 20 mg OD (n = 472)	8 wk	Novartis Pharma		✓	✓
Kang et al,[25] 2019	Multicenter, randomized, double-blind	118 with HFpEF	200 mg BID (n = 60)	Valsartan 160 mg BID (n = 58)	12 mo	Novartis Pharma			✓
Solomon et al,[26] 2019	Multicenter, randomized, double-blind	804 (12.7%)	200gm BID (n = 297)	Valsartan 160 mg BID (n = 310)	Median of 39 mo	Novartis Pharma	✓		
Tsutsui et al,[28] 2021	Multicenter, randomized, double-blind	223 with HFrEF	200 mg BID (n = 111)	Enalapril 10 mg BID (n = 112)	Median of 19 mo	Multiple pharmaceutical companies	✓		✓
Pfeffer et al,[40] 2021	Multicenter, randomized, double-blind	1058 (16.9%) with AMI and HFrEF	200 mg BID (n = 475)	Ramipril 5 mg BID (n = 478)	Median of 23 mo	Novartis Pharma	✓		
Wang et al,[29] 2021	Single-center, parallel-group	137 with AMI and HFrEF	100 mg BID (n = 68)	Enalapril 5 mg BID initially (n = 69)	6 mo	no conflict of interest declared	✓		
Zhang et al,[30] 2021	Single-center, parallel-group	156 with STEMI	Uptitrated as tolerated to 200 mg BID (n = 79)	Perindopril uptitrated as tolerated (n = 77)	6 mo	no conflict of interest declared	✓		
Rakugi et al,[41] 2022	Multicenter, randomized, double-blind,	1161 with hypertension	400 mg/d (n = 385)	Olmesartan 20 mg OD (n = 389)	8 wk	Novartis		✓	✓

AMI=acute myocardial infarction; BID=twice a day; BP=blood pressure; HFpEF=heart failure preserved ejection fraction; HFrEF=heart failure reduced ejection fraction; MACEs=major adverse cardiovascular events; OD=once daily; RCT=randomized controlled trial.

Risk of Bias in Included Studies

The RoB-2 tool was used to assess risk of bias for each of the included studies. Table 2 shows a summary of these assessments. Overall, there were concerns about risk of bias for four of the included studies.

Major Adverse Cardiovascular Events

Six RCTs involving 3887 Asians compared the risk of MACEs between sacubitril/valsartan and control. These RCTs initially gave sacubitril/valsartan as low dose and uptitrated to achieve a dose of 400 mg per day. Active controls were also uptitrated to the maximum recommended dose.

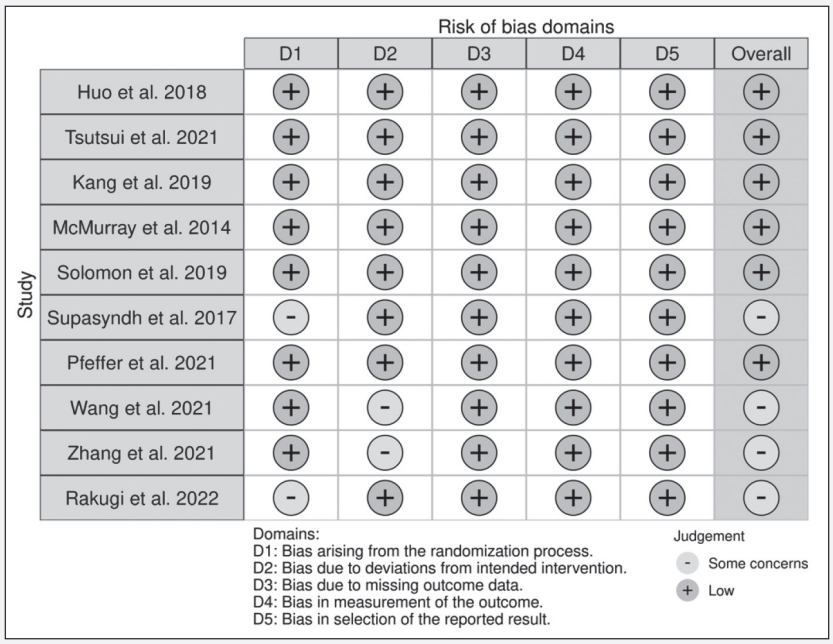
Three of the trials have a low risk of bias, and the other three have "some concerns" for risk of bias based on the RoB-2 tool primarily because of lack of information on blinding methods for Wang et al[29] and Zhang et al.[30] As seen in Figure 2.1, the overall pooled estimate showed that sacubitril/valsartan did not significantly reduce the risk for MACEs in Asians compared with control (HR, 0.94; CI, 0.81–1.10; $P = 0.45$) with an I^2 of 0%. Subgroup analysis further showed a trend toward MACE reduction among Asians with heart failure with reduced ejection fraction, but it was not statistically significant (HR, 0.89; CI, 0.73–1.08; $P = 0.22$; $I^2 = 0\%$); similar results were seen with acute myocardial infarction (HR, 0.90; CI, 0.65–1.24; $P = 0.50$; $I^2 = 0\%$). One study reported MACEs in heart failure with preserved ejection fraction, which was not statistically significant (HR, 1.25; CI, 0.87–1.80; $P = 0.23$; $I^2 = 0\%$).

Sensitivity analysis shown in Figure 2.2 revealed similar results with the primary analysis for the reduction of the risk for MACEs in Asians (HR, 0.96; CI, 0.81–1.13; $P = 0.63$; $I^2 = 12\%$).

BP Control Outcome

Three RCTs determined the effect of sacubitril/valsartan on blood pressure control in 2308 Asians with mild to moderate hypertension. Two trials included for this outcome had "some

Table 2. Risk of Bias of Included Studies Using RoB-2



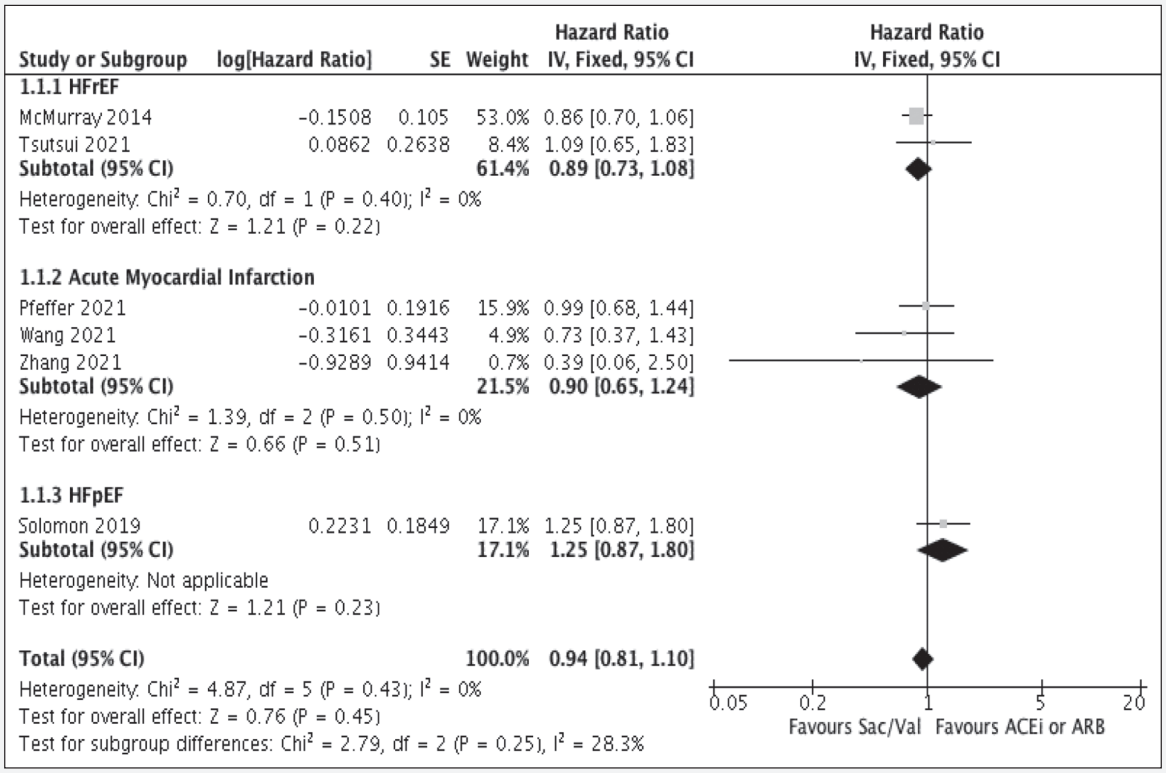


Figure 2.1. Forest plot for the outcome of MACEs.

ACEi=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; CI=confidence interval; HFpEF=heart failure preserved ejection fraction; HFrEF=reduced ejection fraction heart failure; IV=inverse variance; MACEs=major adverse cardiovascular events; Sac/Val=sacubitril/valsartan.

concerns" for the risk of bias primarily because of lack of allocation concealment. All three trials compared 400 mg/d of sacubitril/valsartan against olmesartan given 20 mg daily. As shown in Figure 3, pooled analysis of results showed that treating with sacubitril/valsartan at 400 mg/d was significantly associated with blood pressure control within a follow-up of 8 to 14 weeks (OR, 1.63; CI, 1.38–1.92; $P < 0.00001$; $I^2 = 7\%$).

Safety Outcomes

Asian data for adverse events are available from five studies for SAEs and seven studies for nonserious adverse events involving a total of 4258 participants. Three of the articles were assessed to have a low risk of bias, whereas four were determined to have "some concern" for bias primarily because of vague treatment allocation concealment methods. As seen in Figure 4, sacubitril/valsartan is determined to have an overall insignificant association for SAEs (OR, 0.94; CI, 0.63–1.41; $P = 0.77$; $I^2 = 46\%$).

Figure 5 shows that sacubitril/valsartan was insignificantly associated with nonserious adverse events overall (OR, 0.98; CI, 0.86–1.11; $P = 0.72$; $I^2 = 46\%$). Subgroup analysis showed a significantly increased odds for hypotension (OR, 1.59; CI, 1.19–2.13; $P = 0.002$; $I^2 = 0\%$) and dizziness (OR,

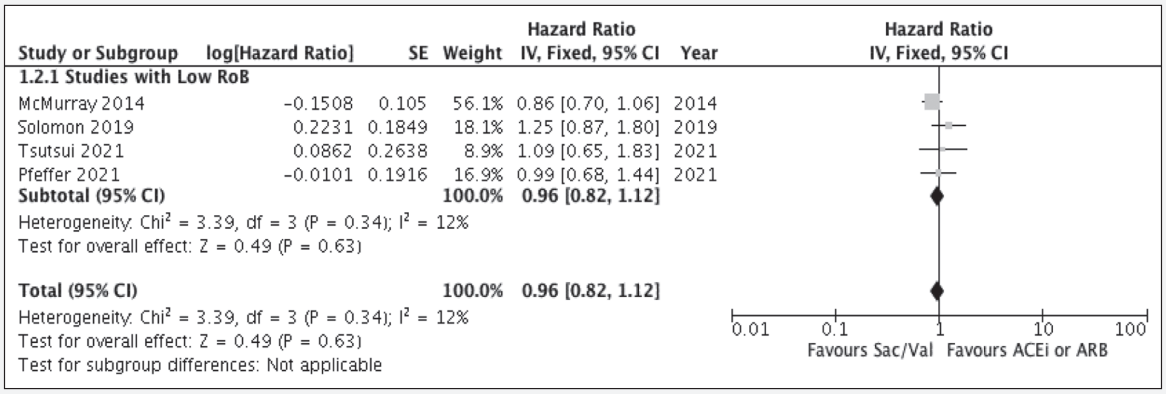


Figure 2.2. Sensitivity analysis for the outcome of major adverse cardiovascular events.
ACEi=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; CI=confidence interval; df=degrees of freedom; IV=inverse variance; RoB=risk of bias; Sac/Val=sacubitril/valsartan.

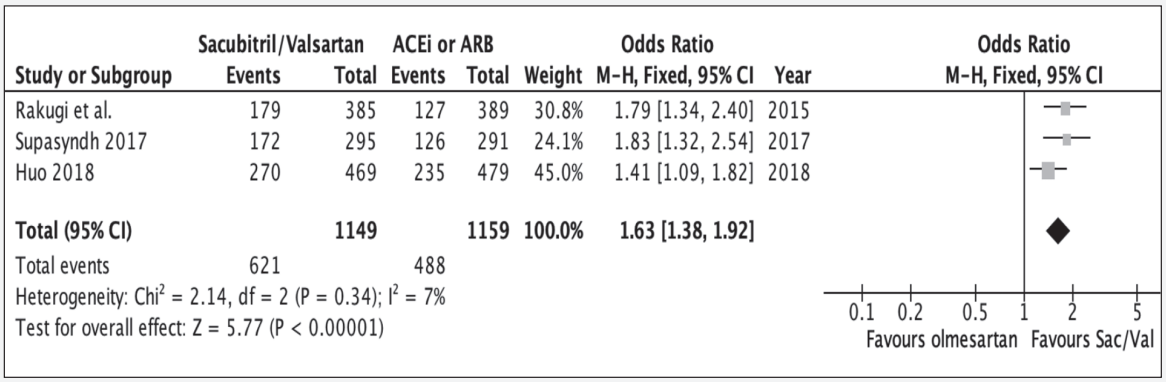


Figure 3. Forest plot for the outcome of blood pressure control.
CI=confidence interval; df=degrees of freedom; M-H=Mantel-Haenszel; Sac/Val=sacubitril/valsartan.

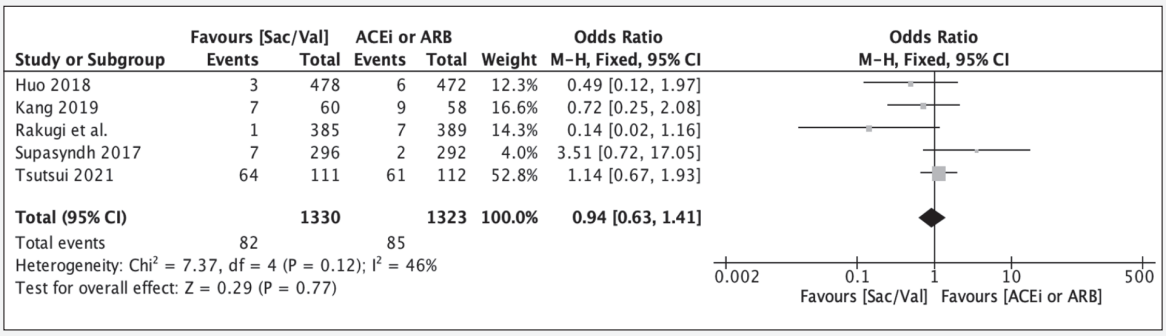


Figure 4. Forest plot for safety outcome, SAEs.
ACEi=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; CI=confidence interval; df=degrees of freedom; M-H=Mantel-Haenszel; Sac/Val=sacubitril/valsartan; SAEs=serious adverse events.

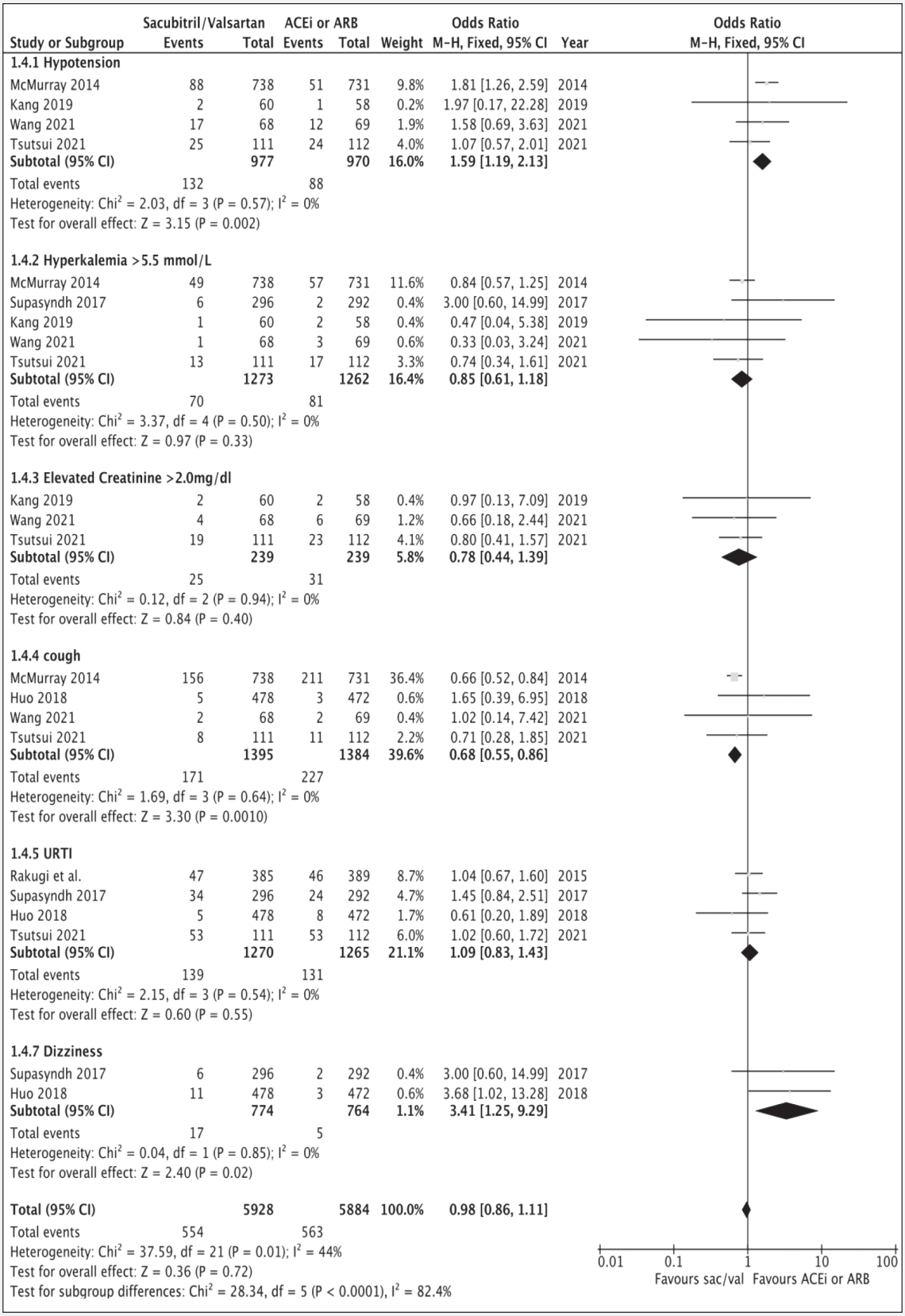


Figure 5. Forest plot for the outcome of safety outcome, nonserious adverse events.
ACEi=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; CI=confidence interval; df=degrees of freedom; M-H=Mantel-Haenszel; sac/val=sacubitril/valsartan; URTI=upper respiratory tract infection.

3.54; CI, 1.61–7.81; $P = 0.002$; $I^2 = 0\%$) with sacubitril/valsartan. In contrast, there is a significant odds reduction for cough compared with conventional ACEi/ARB (OR, 0.70; CI, 0.56–0.87; $P = 0.002$; $I^2 = 0\%$). Pooled data also showed that there were insignificant associations between treatment with sacubitril/valsartan and hyperkalemia, elevated creatinine, and upper respiratory tract infection.

Publication Bias

The fixed-effects funnel plots of each synthesis are seen in Figure 6. There are no statistically significant differences between studies for MACEs (Kendall $\tau = -0.13$, $P = 0.71$; Egger degrees of freedom [*df*] = 4.00, $P = 0.861$), blood pressure control (Kendall $\tau = 0.80$, $P = 0.17$; Egger *df* = 2.00, $P = 0.06$), severe adverse events (Kendall $\tau = -0.40$, $P = 0.25$; Egger *df* = 4.00, $P = 0.35$), and nonsevere adverse events (Kendall $\tau = 0.02$, $P = 0.89$; Egger *df* = 23.00, $P = 0.17$).

Certainty Assessment

Compared with active control, evidence indicates that sacubitril/valsartan may have little to no effect on reduction of MACEs in Asians with moderate certainty. The evidence was downgraded one step for imprecision because the confidence interval was consistent with appreciable benefit and appreciable harm. On the other hand, with certainty of evidence, sacubitril/valsartan significantly increases the odds of blood pressure control compared with active control.

DISCUSSION

All studies included are RCTs involving Asian patients from China, India, Japan, Philippines, Singapore, South Korea, Taiwan, and Thailand. The results of this study contradict previous meta-analyses by Geng et al[11] (OR, 0.78; 95% CI, 0.69–0.88; P < 0.05) and Yuqin et al[43] (RR, 0.89; 95% CI, 0.83–0.96), which showed strong benefits with the use of sacubitril/valsartan in patients with heart failure with reduced

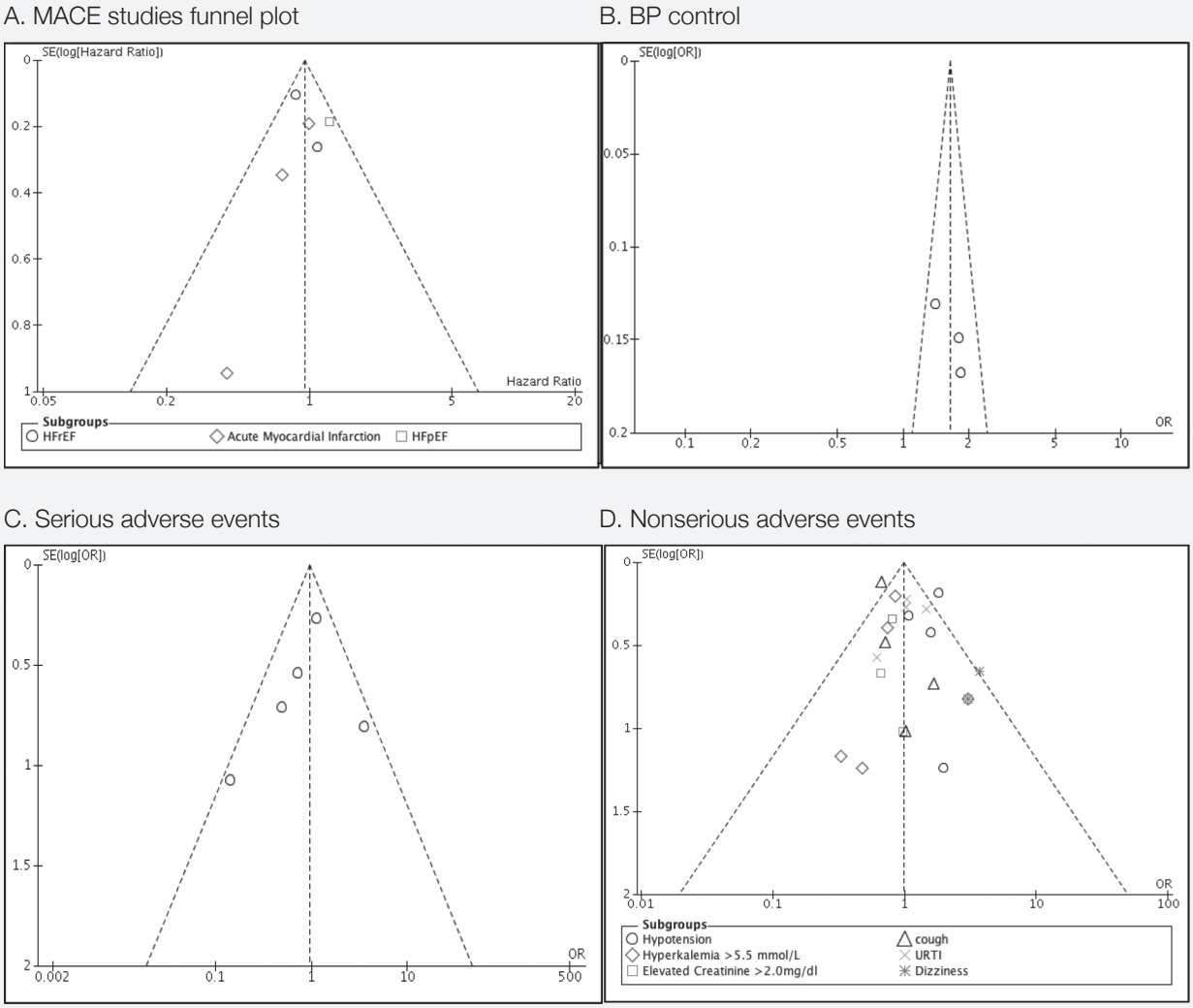


Figure 6. Funnel plots for MACEs, BP control, and Safety (serious and nonserious adverse events).
BP=blood pressure; HFpEF=heart failure preserved ejection fraction; HFrEF=reduced ejection fraction heart failure; MACEs=major adverse cardiovascular events; URTI=upper respiratory tract infection.

ejection fraction.[42,43] Results of the subgroup analysis in this study also contradict the meta-analysis by Zhao et al,[44] which reported that sacubitril/valsartan significantly reduced the risk for MACEs (RR, 0.61; CI, 0.46–0.82; $P = 0.001$) in patients with acute myocardial infarction.[44] The contrast of the results for Asians as shown in this study could be due to several reasons. First, certain comorbidities bring Asians at higher risk for adverse cardiovascular events compared with other ethnicities. In the United States, Asians have been determined to have the highest smoking rates and have more nontraditional cardiovascular risk factors such as elevated inflammatory markers and insulin resistance compared with non-Hispanic Whites, African Americans, and non-White Hispanics.[45] In 2014, the World Health Organization Global Status Report revealed that the prevalence rates of hypertension, diabetes/glucose intolerance, and smoking in Southeast Asians were almost twice higher (>24% in Cambodia and Laos) compared with the United Kingdom (15.2%) or the United States (13.4%).[46] These ethnic disparities in cardiovascular risk factors have translated into higher premature death rates from noncommunicable diseases (chiefly cardiovascular disease) in the Philippines (27.0%), Myanmar (24.3%), Indonesia (23.1%), and Laos (24.2%) compared with the United Kingdom (12.0%).[46,47] Second, a deeper understanding of the pharmacogenetic differences among patient populations have placed Asians at higher risk for decreased drug efficacy and toxicities.[48] In the case of sacubitril, this drug is activated by an enzyme encoded by *carboxylesterase gene 1 (CES1)* which is also involved in the metabolism of other medications such as methylphenidate, clopidogrel, oseltamivir, and enalapril.[48,49] Significant interindividual variability in *CES1* expression has been associated with decreased or increased drug metabolism, depending on the gene variant.[49] Available studies have determined that the *CES1A2* variant has been associated with increased metabolism, whereas the *G143E* variant has been associated with impaired activation.[49,50] However, the correlation of these variants to clinical outcomes remains to be explored.

This meta-analysis showed that treatment with sacubitril/valsartan significantly increased the odds of blood pressure control compared with olmesartan 20 mg once daily among Asians. Olmesartan is a widely used antihypertensive in the included population of the three studies and is considered a potent ARB with a safety and efficacy profile similar to those of other ARBs.[18,27,41] Our study result is consistent with another meta-analyses and may be the result of increased sodium excretion, vasodilatation, and aldosterone suppression.[11,51,52]

The safety analysis in this study is consistent with a recent meta-analysis by Huang et al,[38] which showed that treatment with sacubitril/valsartan was not associated with a significant risk for SAEs and nonserious adverse events.[38] Our meta-analysis is also consistent with other meta-analyses that there is a significant risk for hypotension with sacubitril/valsartan treatment and that Asians, in particular, have a significant risk for developing dizziness during treatment.[24,38] Likewise, the significant reduction in the risk for developing cough during treatment with sacubitril/valsartan compared with ACEi/ARB is also congruent with previous studies.[24,38]

CONCLUSIONS

The efficacy of sacubitril/valsartan in reducing MACEs in Asians is not statistically significant, although there is a trend toward benefit. Sacubitril/valsartan is strongly associated with better hypertension control against olmesartan 20 mg/d. Finally, the overall safety profile of sacubitril/valsartan is not significantly different against conventional ACEi/ARBs, but it is significantly associated with an increased risk for hypotension and dizziness with a lower risk for cough occurrence.

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