

## Review Article



# Sacubitril/Valsartan in Asian Patients with Heart Failure with Reduced Ejection Fraction

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## ABSTRACT

The Prospective comparison of Angiotensin Receptor-neprilysin inhibitor (ARNI) with Angiotensin converting enzyme inhibitor (ACEI) to Determine Impact on Global Mortality and morbidity in Heart Failure (HF) trial (PARADIGM-HF) showed that adding a neprilysin inhibitor (sacubitril) to a renin-angiotensin system blocker (and other standard therapy) reduced morbidity and mortality in ambulatory patients with chronic HF with reduced ejection fraction (HFrEF). In PARADIGM-HF, valsartan combined with sacubitril (a so-called ARNI) was superior to the current gold standard of an ACEI, specifically enalapril, reducing the risk of the primary composite outcome of cardiovascular (CV) death or first HF hospitalization by 20% and all-cause death by 16%. Following the results of PARADIGM-HF, sacubitril/valsartan was approved by American and European regulatory authorities for the treatment of HFrEF. The burden of HF in Asia is substantial, both due to the huge population of the region and as a result of increasing CV risk factors and disease. Both the prevalence and mortality associated with HF are high in Asia. In the following review, we discuss the development of sacubitril/valsartan, the prototype ARNI, and the available evidence for its efficacy and safety in Asian patients with HFrEF.

**Keywords:** Asians; Sacubitril/valsartan; Heart failure

## INTRODUCTION

Heart failure (HF) is a major global public health problem affecting an estimated 26 million people around the world.<sup>1)</sup> Asia accounts for more than 60% of the global population and more than two-thirds of the continent's countries are categorized as low- and middle-income countries. The increasing burden of cardiovascular (CV) disease in Asia is usually attributed to the increasing prevalence of risk factors such as obesity and diabetes.<sup>2-4)</sup> Consequently, the burden of HF has also increased, with prevalence estimates in Asia ranging from 1–5%, compared to 1–2% in Europe and North America. The overall prevalence in is estimated to be 4.2 million in China and 1.3–4.6 in India.<sup>2-5)</sup> Moreover, unlike the West, where HF incidence rates have been stabilizing, the incidence of HF continues to rise in Asia, with an estimated 500,000 new cases in China alone and another 0.5–1.8 million new cases in India each year.<sup>3)</sup> As a result of its large population, and the changing epidemiology of CV risk factors and disease in the region, more people are now living with HF in Asia than anywhere else in the world.

**Author Contributions**

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Of added concern, Asian patients with HF are younger and show worse survival than the global average.<sup>2)3)</sup> It has also been suggested that there may be differences between Asians and other races in the tolerability, efficacy and safety of CV drugs, potentially diminishing their value.<sup>6)7)</sup>

The most recent breakthrough in the pharmacological management of HF was the demonstration that adding a neprilysin inhibitor (sacubitril) to a renin-angiotensin system blocker (and other standard therapy) reduced morbidity and mortality in patients with chronic, symptomatic, ambulatory HF with reduced ejection fraction (HFrEF). In the Prospective comparison of Angiotensin Receptor-neprilysin inhibitor (ARNI) with Angiotensin converting enzyme inhibitor (ACEI) to Determine Impact on Global Mortality and morbidity in HF trial (PARADIGM-HF), valsartan combined with sacubitril (ARNI) was superior to the current gold standard of an ACEI, specifically enalapril, reducing the risk of the primary composite outcome of CV death or first HF hospitalization by 20% and all-cause death by 16%.<sup>8)</sup> The results of PARADIGM-HF led to the approval of sacubitril/valsartan by American and European regulatory authorities, among others, for the treatment of HFrEF and its recommendation in international guidelines.<sup>9)10)</sup>

In light of the considerable burden of HFrEF and disease associated mortality in Asia, the purpose of this article is to review the development of ARNIs and the evidence for their efficacy and safety in Asian patients with HFrEF.

## NATRIURETIC PEPTIDES AND NEPRILYSIN

Myocardial damage, most commonly as a result of poorly controlled hypertension, myocardial ischaemia or infarction, results in activation of the renin-angiotensin-aldosterone system (RAAS). Whilst initially compensatory to help maintain cardiac output, prolonged and sustained RAAS activation can have detrimental effects including increasing cardiac afterload due to vasoconstriction, promoting myocardial fibrosis and fluid retention secondary to an anti-natriuretic action. Ultimately these processes become deleterious and result in the development of the syndrome of HF and its progressive worsening over time.

The natriuretic peptides (NPs) are a family of vasoactive peptides which are released by the heart, in response to increased myocardial wall stress, and from blood vessels and the kidneys. The NPs help to nullify the harmful effects of an overactive RAAS. The first NP to be described was atrial NP (ANP), when in 1981, de Bold et al.<sup>11)</sup> demonstrated the increased urinary sodium and water excretory effect of atrial extracts. Subsequently, B-type NP (BNP), C-type NP (CNP) and urodilatin were identified, sharing the beneficial vasodilatory, natriuretic, anti-fibrotic and anti-hypertrophic properties of ANP.<sup>12)</sup>

The potential benefits of the NPs, including amelioration of the effects of RAAS overactivity, led to several lines of research into how these peptides might be used therapeutically. One obvious approach was short-term intravenous administration of supra-physiological doses of *exogenous* NP in patients hospitalised with decompensated HF. However, in 2 trials neither nesiritide (a recombinant form of BNP) nor ularitide (a recombinant form of urodilatin) reduced mortality or re-hospitalization.<sup>13)14)</sup>

The alternative, and ultimately successful, approach was to augment level of *endogenous* NPs by reducing their elimination which occurs through 2 major pathways. One is through a NP

clearance receptor (NPRC or NPRC3) and the other is through degradation by the enzyme neprilysin (also known as membrane metallo-endoropeptidase or neutral endopeptidase [NEP]), a membrane bound endopeptidase found in many tissues, most prominently in the kidney.<sup>15)16)</sup>

It is important to note that neprilysin also plays a role in the degradation several other peptides including bradykinin, adrenomedullin, substance P and calcitonin, apelin, glucagon-like peptide-1, vasoactive intestinal peptide, and enkephalins and these other substrates may contribute to the benefits of neprilysin inhibition.<sup>17)18)</sup>

## NEPRILYSIN INHIBITION

Roques and colleagues in 1980 reported the first neprilysin inhibitor, thiorphan in animal models with demonstration of favourable hemodynamic and hormonal responses.<sup>19)20)</sup> Early reports showed that acute inhibition of neprilysin with oral racecadotril (formerly acetorphan) and intravenous candoxatrilat demonstrated stimulation of natriuresis and diuresis along with increases in circulating ANP levels in humans without any associated deleterious activation of RAAS or sympathetic activity as observed with loop diuretics.<sup>21-24)</sup> Furthermore, it was also seen that candoxatrilat and ecadotril reduced pulmonary capillary wedge pressure in patients with HF.<sup>21)23)</sup>

However, it was subsequently demonstrated that chronic dosing with candoxatril did not lead to a sustained reduction in blood pressure and development of the drug was consequently halted.<sup>25)</sup> The amelioration of the hypotensive action of this agent likely resulted from accumulation of angiotensin II, the breakdown of which was inhibited by candoxatril, and which offset the vasodilatory effects of NP accumulation.<sup>26)27)</sup> In retrospect, this finding demonstrated the need to combine neprilysin inhibition with blockade of the renin-angiotensin system.

## ANGIOTENSIN CONVERTING ENZYME-NEUTRAL ENDOPEPTIDASE INHIBITION

The first approach to combining neprilysin inhibition with renin-angiotensin system blockade was using molecules that inhibited both ACE and NEP, the most studied of which was omapatrilat.<sup>28)</sup>

In the Inhibition of Metalloprotease by Omapatrilat in a Randomized Exercise and Symptoms Study (IMPRESS) in HF trial, omapatrilat was compared to lisinopril to assess for improvement in functional capacity and clinical outcomes in 573 patients with HFrEF.<sup>29)</sup> While there was no significant difference seen in the primary outcome of exercise tolerance, a positive trend was seen in favour of omapatrilat in reducing the composite of death, admission or discontinuation of study treatment for worsening HF.

Two years later, the results of the Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events (OVERTURE) trial, a randomised controlled trial of omapatrilat 40 mg once daily compared to enalapril 10 mg twice daily, were published.<sup>30)</sup> There was no benefit of omapatrilat over enalapril in reduction of the primary endpoint of all-cause death or HF hospitalization. However, a nominally statistically significant 9% reduction in the secondary

endpoint of all-cause death and CV hospitalization was seen in patients randomized to receive omapatrilat. Moreover, in a post hoc analysis of the primary end point using the definition used in the Studies Of Left Ventricular Dysfunction (SOLVD) treatment trial there was an 11% lower risk in patients treated with omapatrilat (nominal,  $p=0.012$ ).<sup>30</sup> In retrospect, it also appeared that the single large daily dose of omapatrilat used in OVERTURE led to excessive hypotension and study drug discontinuation, while at the same time failed to provide sustained 24-hour inhibition of either neprilysin or the renin-angiotensin system. Together, these considerations suggested that, used in the right way, combined neprilysin and renin-angiotensin system inhibition might still be useful in HF. However, further development of omapatrilat was halted because of an excessively high rate of serious angioedema, particularly in the Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril trial (OCTAVE) in hypertension where 2.2% of patients randomized to omapatrilat had angioedema compared to 0.7% of those randomized to enalapril.<sup>31</sup> The higher rate of angioedema observed with omapatrilat was felt to be secondary to the accumulation of bradykinin, resulting from combined ACE and neprilysin inhibition (because both enzymes breakdown bradykinin). Omapatrilat was later found to also inhibit aminopeptidase-P, another key enzyme involved in degradation of bradykinin.<sup>32</sup>

## ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITORS

The solution to the problem of safely combining neprilysin and renin-angiotensin system inhibition was solved by using an angiotensin receptor blocker (ARB), instead of an ACE inhibitor, and the development of sacubitril/valsartan.

Sacubitril/valsartan (originally named LCZ696) is the first in class ARNI, and is a 1:1 combination of AHU377 (sacubitril) and an ARB (valsartan).<sup>33</sup> Upon oral administration, sacubitril/valsartan dissociates and sacubitril is converted to its active metabolite sacubitrilat. Sacubitrilat and valsartan have half-lives of approximately 12 and 9.9 hours respectively and given twice daily ensure sustained neprilysin and RAAS inhibition over the 24-hour period.<sup>34</sup> The valsartan formulation in sacubitril/valsartan is more bioavailable than conventional valsartan, with a 40% higher systemic exposure per mg of drug.<sup>35</sup> Consequently, the target dose of sacubitril/valsartan (97/103 mg twice daily) gives plasma concentrations of valsartan equivalent to 160 mg twice daily of the conventional compound (the dose as studied in the Valsartan Heart Failure Trial [Val-HeFT]).<sup>36</sup> This dose also gives a sustained increase in cyclic guanosine monophosphate, reflecting the second-messenger response to the increase in natriuretic (and possibly other) peptides resulting from neprilysin inhibition by sacubitrilat.<sup>37</sup>

## PROSPECTIVE COMPARISON OF ANGIOTENSIN RECEPTOR-NEPRILYSIN INHIBITOR WITH ANGIOTENSIN CONVERTING ENZYME INHIBITOR TO DETERMINE IMPACT ON GLOBAL MORTALITY AND MORBIDITY IN HEART FAILURE (PARADIGM-HF) TRIAL

PARADIGM-HF was designed to test the efficacy and safety of adding a neprilysin inhibitor (sacubitril) to a renin-angiotensin system blocker (and other standard therapy), compared with a renin-angiotensin system blocker (and other standard therapy) alone. Specifically,

**Table 1.** Characteristics of large trials in HF with enalapril

Trial	No. of patients assigned to enalapril	Target dose (mg)	Mean daily dose (mg)
CONSENSUS (1987) <sup>54)</sup>	127	20 bid	18.4
SOLVD-T (1991) <sup>38)</sup>	1,285	10 bid	16.6
SOLVD-P (1992) <sup>55)</sup>	2,111	10 bid	16.7
V-HeFT II (1991) <sup>56)</sup>	403	10 bid	15.0
OVERTURE (2002) <sup>30)</sup>	2,884	10 bid	17.7
CARMEN (2004) <sup>57)</sup>	190 enalapril only	10 bid	16.8
	191 enalapril plus carvedilol	10 bid	14.9
CIBIS-3 (2005) <sup>58)</sup>	505 enalapril first	10 bid	17.2
	505 bisoprolol first	10 bid	15.8
ATMOSPHERE (2016) <sup>59)</sup>	2,336 enalapril only	5–10 bid	18.6
	2,340 aliskiren plus enalapril	5–10 bid	19.1

ATMOSPHERE = Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure; CARMEN = Carvedilol ACE-Inhibitor Remodelling Mild CHF Evaluation; CIBIS = Cardiac Insufficiency Bisoprolol Study; CONSENSUS = Cooperative North Scandinavian Enalapril Survival Study; HF = heart failure; OVERTURE = Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events; SOLVD = Studies Of Left Ventricular Dysfunction; V-HeFT = Vasodilator-Heart Failure Trial.

sacubitril/valsartan 97/103 mg twice daily was compared to enalapril 10 mg twice daily.<sup>8)</sup> The choice of comparator, enalapril 10 mg twice daily, was based on the evidence from the SOLVD-Treatment trial, the only large-scale, long-term, trial in a broad ambulatory HFrEF population, demonstrating superiority of an ACE inhibitor compared to placebo in reducing morbidity and mortality in HFrEF.<sup>38)</sup> For this reason enalapril 10 mg twice daily has been the “gold-standard” comparator in other trials and is the most studied ACE inhibitor in HFrEF trials (**Table 1**).

Patients were recruited between 2009 and 2012. All patients underwent a sequential run-in period first with enalapril 10 mg twice daily followed by sacubitril/valsartan 97/103 mg twice daily for a total of 6–8 weeks. If no unacceptable side-effects were seen, patients were randomized 1:1 in a double-blind fashion to either sacubitril/valsartan 97/103 mg twice daily or enalapril 10 mg twice daily and followed up for occurrence of prespecified outcomes (or adverse events). PARADIGM-HF was terminated early in March 2014 on the recommendation of the Data Monitoring Committee due to overwhelming benefit observed with sacubitril/valsartan therapy. The median duration of follow-up in PARADIGM-HF was 27 months.

## CLINICAL EFFICACY OF SACUBITRIL/VALSARTAN IN PARADIGM-HF

Sacubitril/valsartan significantly reduced the risk of the primary composite outcome (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.73–0.87) and each of its components i.e. CV death (HR, 0.80; 95% CI, 0.71–0.89) and HF hospitalization (HR, 0.79; 95% CI, 0.71–0.89). Equal and significant reductions in the risk of the 2 major modes of CV death, sudden death and death from worsening HF, were also observed, and there was a 16% (95% CI, 7–24%) reduction in the risk of all-cause mortality.<sup>39)</sup>

Hence, for every 1,000 patients switched from enalapril to sacubitril/valsartan, there would be 46 fewer primary composite endpoint events, 27 fewer first HF hospitalisations, 31 fewer CV deaths and 28 fewer deaths from any cause over a follow-up of 27 months.

In addition, subsequent post-hoc analyses of PARADIGM-HF have shown no difference in the benefit of therapy with sacubitril/valsartan compared to enalapril according to age or to geographical region of enrolment (which will be discussed more with respect to Asia in later

sections).<sup>40,41)</sup> No other significant treatment effect interactions were seen in any of the other prespecified sub-groups or in relation to background drug or device therapy.<sup>8,42)</sup>

## SAFETY AND TOLERABILITY OF SACUBITRIL/VALSARTAN IN PARADIGM-HF

Patients randomized to sacubitril/valsartan had significantly more hypotension than patients randomized to enalapril (14% vs. 9%;  $p < 0.001$ ) even though study-drug discontinuation as a result of hypotension was very rare and not significantly different between the treatment groups (0.9% vs. 0.7%;  $p = 0.380$ ). No significant difference in the rate of angioedema was reported (19 patients vs. 10 patients;  $p = 0.130$ ). Renal dysfunction, hyperkalaemia and cough were less commonly reported with sacubitril/valsartan compared to enalapril. Dementia and cognition related adverse events were not increased by sacubitril/valsartan in PARADIGM-HF.<sup>43)</sup>

## REGULATORY APPROVAL AND STATISTICAL ROBUSTNESS OF RESULTS

The results of PARADIGM-HF were swiftly followed by regulatory approval of sacubitril/valsartan for use in patients with HFrEF and conforming to the main inclusion criteria used in the trial. Regulatory approval of a new drug requires that its effectiveness and safety be demonstrated in either 2 trials with a 2-sided  $p$  value  $< 0.05$ , or a single, large, internally consistent multicentre study with a  $p$  value  $< 0.00125$ . PARADIGM-HF was a large (8,399 patients), highly statistically significant ( $p$  value = 0.0000004), internally consistent (lack of subgroup interaction), multicentre (sites in 47 countries) study with large treatment effects on morbidity and mortality. As a result of the robustness of the results of PARADIGM-HF it has been considered unethical to conduct a second large clinical trial with sacubitril/valsartan in patients HFrEF. With a  $p$  value of 0.0000004 for the primary composite outcome, the chance that sacubitril/valsartan is not superior to enalapril is less than one in a million.<sup>44)</sup>

On the basis of a single trial providing evidence of benefit, the American College of Cardiology (ACC) and the European Society of Cardiology guidelines have afforded sacubitril/valsartan a class I, level of evidence B treatment recommendation for use in HFrEF to reduce HF hospitalization and mortality in patients who remain symptomatic despite pharmacotherapy with ACE/ARB, a beta blocker and a mineralocorticoid antagonist.<sup>9,10)</sup> A meta-analysis of the 3 trials (PARADIGM-HF, IMPRESS, and OVERTURE) comparing combined neprilysin/RAAS inhibition to RAAS inhibition alone in HFrEF, reported a significant pooled HR in reducing the risk of a composite endpoint of all-cause mortality or HF hospitalisation (HR, 0.86; 95% CI, 0.76–0.97).<sup>45)</sup> Based on the results of this meta-analysis, as well as the degree of statistical certainty of benefit reported in PARADIGM-HF, we believe it can be reasonably argued that the body of evidence in favour of neprilysin inhibition supports a level of evidence A recommendation for treatment with sacubitril/valsartan in patients with symptomatic HFrEF, with now additional support for comparison of sacubitril/valsartan versus Enalapril on Effect on natriuretic peptide (NT-pro-BNP) in patients stabilized from an acute Heart Failure episode (PIONEER-HF; see below).

PARADIGM-HF required patients to be tolerant of a dose of an ACE-inhibitor or ARB equivalent to enalapril 10 mg/day prior to enrolment. Several trials now support the use of sacubitril/valsartan in ACE-inhibitor or ARB naïve patients including those stabilised from presentations

of acutely decompensated HF (a proportion of which we first or “de novo” presentations). The ACC guidance permits prescription of sacubitril/valsartan to ACEI/ARB naïve patients, a strategy which is supported by the results of the TITRATION and TRANSITION studies.<sup>46,47</sup> Sacubitril/valsartan was also found to result in a greater reduction in the N-terminal prohormone of BNP levels, compared to enalapril, among patients hospitalized for acute decompensated HF in the PIONEER-HF trial.<sup>48</sup> A significant reduction in risk of rehospitalization for HF was also seen, although the trial was not powered for clinical outcomes.

There are a number of ongoing studies to assess the efficacy and safety of sacubitril/valsartan in other populations. Among them, the 2 that require mention here are the Prospective Comparison of ARNI with ARB Global Outcomes in HF With Preserved Ejection Fraction (PARAGON-HF; NCT01920711) trial and the Prospective ARNI vs. ACE Inhibitor Trial to Determine Superiority in Reducing HF Events After MI (PARADISE-MI; NCT02924727).<sup>49</sup> PARAGON-HF will evaluate the efficacy of sacubitril/valsartan compared to valsartan in reducing morbidity and mortality in patients with HF with preserved ejection fraction (HFpEF). It is the largest and the most globally representative HFpEF clinical trial to date and the results are expected this year.<sup>50</sup> PARADISE-MI will assess the effect of sacubitril/valsartan compared to ramipril in reducing the occurrence of the composite endpoint of CV death, HF hospitalization and outpatient HF in post-acute MI patients with left ventricular systolic dysfunction and/or pulmonary congestion with no prior history of chronic HF.

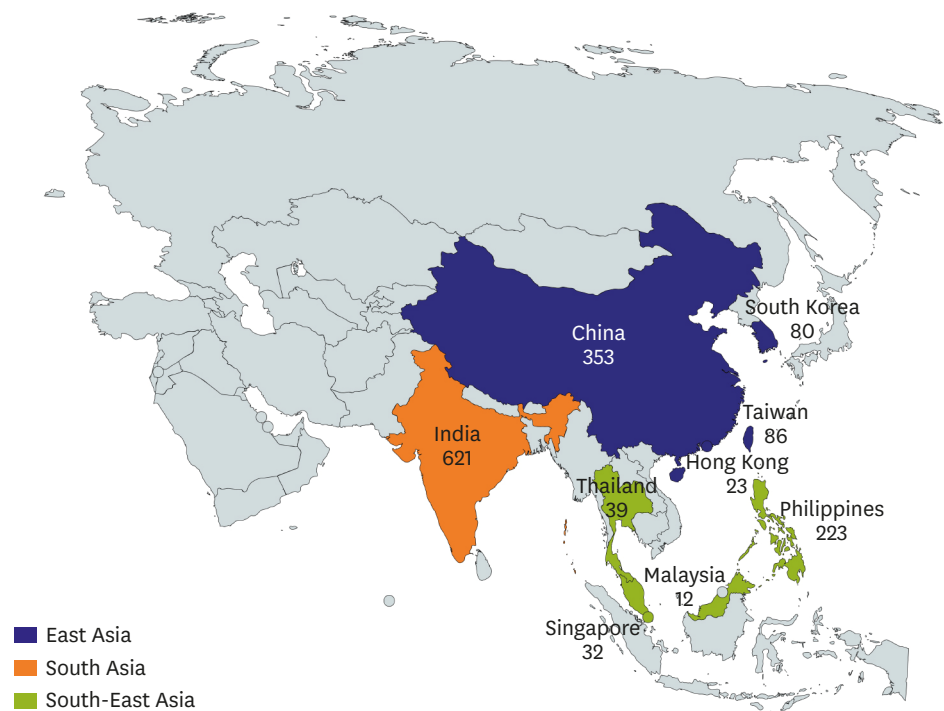
## ASIANS IN THE PARADIGM-HF TRIAL

A total of 1,487 patients were enrolled from 9 countries in the Asia-Pacific region in PARADIGM-HF, accounting for 17.7% of the total cohort.<sup>8</sup> For the purposes of this review, we have further divided Asia in PARADIGM-HF into 3 regions (East, South, and South-East Asia; **Figure 1**) and considered only those living in these countries who self-reported as being of Asian race.

A prior *post-hoc* analysis of PARADIGM-HF by region showed that patients from Asia were the youngest, had the lowest body mass index, lowest systolic blood pressure, reported a better quality of life and had fewer comorbidities.<sup>41</sup> These findings were largely replicated in the Asian subgroups that we have analysed for this review and are shown in **Table 2**. In the analysis presented by Kristensen et al.,<sup>41</sup> patients from Asia were most likely to receive digoxin and less likely to receive all other drugs and device therapies at the time of randomisation. It was also reported that while the risk of the primary composite end-point was highest in patients from Asia compared to North America (HR, 1.39; 95% CI, 1.06–1.80), there was no difference in treatment effect seen overall (p value for interaction-primary composite outcome=0.50).<sup>41</sup>

## CLINICAL EFFICACY OF SACUBITRIL/VALSARTAN IN ASIANS IN THE PARADIGM-HF TRIAL

The Asian patients presented in this analysis were followed up for a median of 26 months. Across all the groups examined, event rates per 100-person years were lower in patients randomized to sacubitril/valsartan compared to enalapril (**Figure 2**). Overall, South Asians had a lower rate of hospitalization for HF and higher mortality when compared to the other groups, and overall mortality due to CV or any cause was highest in Asians compared to the total PARADIGM-HF cohort.



**Figure 1.** Number of patients of Asian patients by region enrolled in PARADIGM-HF (Asian race only). PARADIGM-HF = Prospective comparison of Angiotensin Receptor-neprilysin inhibitor with Angiotensin converting enzyme inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure trial.

Importantly, no difference was seen between the benefits of treatment in Asians and the total PARADIGM-HF cohort or between the different regions of Asia (**Figure 3**).

## TOLERABILITY AND SAFETY OF SACUBITRIL/VALSARTAN IN ASIANS IN THE PARADIGM-HF TRIAL

Concerns regarding potential differences in drug tolerability and safety in Asians, compared to non-Asians, possibly secondary to physical characteristics such as a lower body weight and smaller size, have led the advocacy of lower doses of drugs in Asian patients.<sup>6)</sup> Indeed, the ongoing Prospective comparison of ARNI with ACE inhibitor to determine the novel beneficial treatment value in Japanese Heart Failure patients (PARALLEL-HF) trial in Japanese patients with HFrEF has lower run-in doses for both sacubitril/valsartan (100 mg BD with no up-titration) and enalapril (5 mg BD).<sup>51)</sup> However, the achieved doses of the 2 study treatments in PARADIGM-HF were similar in Asians to those in the overall trial patients. Mean daily dose of sacubitril/valsartan was 374.7±62.7 mg in the entire PARADIGM-HF cohort (compared with a target dose of 400 mg daily). The achieved daily dose was 373.88±66.0 mg in all Asians, 367.6±69.5 mg in East Asians, 374.2±71.8 mg in South Asians and 384.4±41.3 mg in South-East Asians. The mean daily dose of enalapril was 18.9±2.9 mg in PARADIGM-HF overall, and 19.0±2.9 mg, 18.8±3.1 mg, 19.1±2.9 mg, and 17.1±2.3 mg, in the Asian patient groups described above.

The reportedly high incidence of cough with ACEIs in Asians has led to ARBs becoming the preferred means of blocking the renin-angiotensin system in these individuals with HF or



**Table 2.** Baseline characteristics of all patients and by Asian regions enrolled in PARADIGM-HF

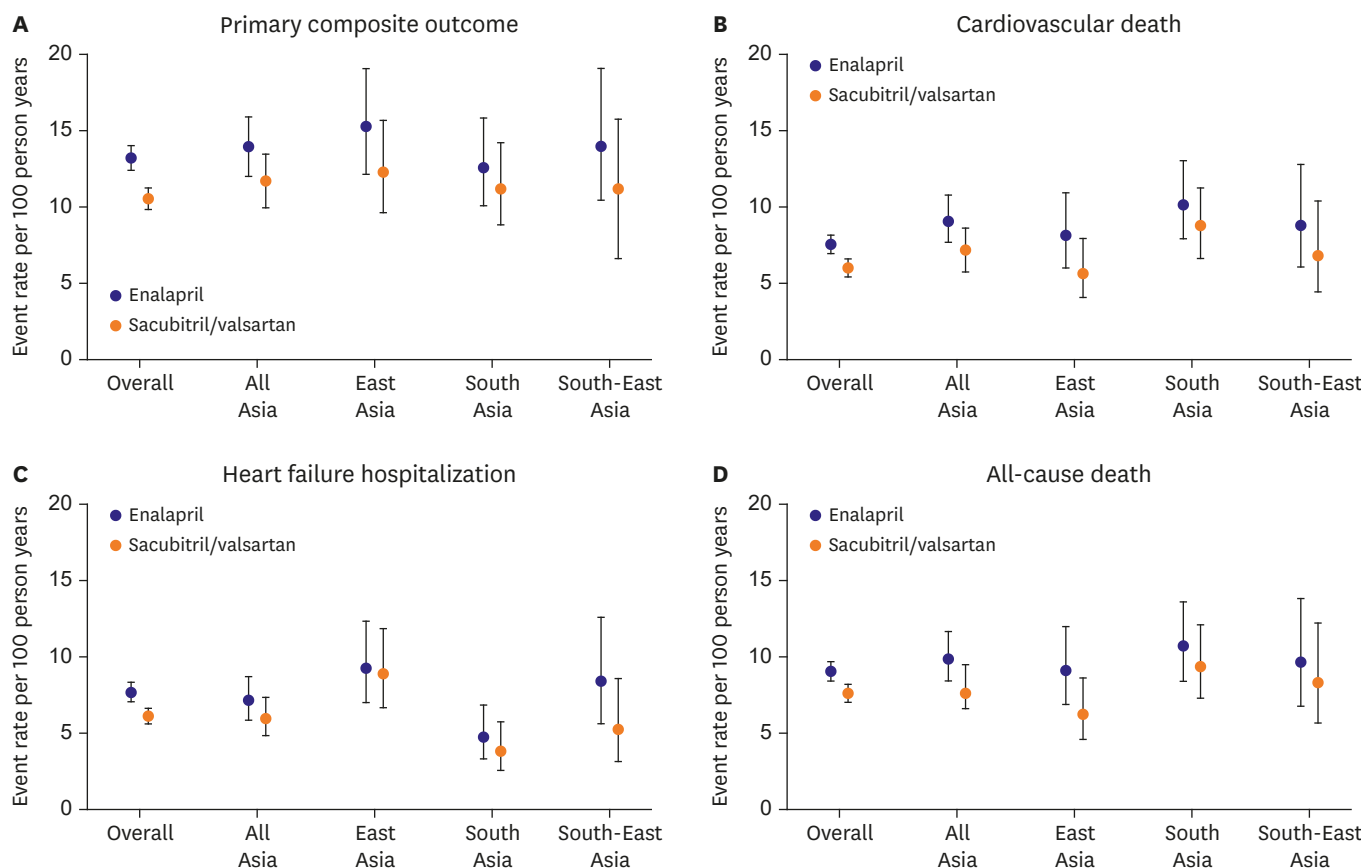
	Overall (n=8,399)	All Asia (n=1,469)	East Asia (n=542)	South Asia (n=621)	South-East Asia (n=306)
Age (years)	63.8±11.4	57.8±11.9	59.7±11.9	57.1±11.7	56.0±11.8
Sex (female)	1,832 (21.8)	287 (19.5)	96 (17.7)	134 (21.6)	57 (18.6)
SBP (mmHg)	121±15	117±15	116±14.6	117±13	119±17
Heart rate (bpm)	72±12	75±11	73±12	77±9	75±13
BMI (kg/m <sup>2</sup> )	28.1±5.5	24.3±4.1	25.0±3.8	23.5±3.9	24.6±4.8
Serum creatinine (mg/dL)	1.12±0.3	1.06±0.3	1.05±0.3	1.03±0.3	1.15±0.3
Clinical features of HF					
Ischemic cardiomyopathy	5,036 (60.0)	855 (58.2)	209 (38.6)	449 (72.3)	197 (64.4)
LVEF (%)	29.5±6.2	28.1±5.9	29.5±5.3	27.5±5.8	27.0±6.6
Median NT-proBNP (pg/mL)	1,615 (888–3,231)	1,731 (914–3,700)	1,775 (934–3,828)	1,530 (832–3,105)	2,147 (1,077–4,679)
Median KCCQ CSS	80 (63–92)	89 (79–96)	91 (82–97)	87 (77–96)	89 (71–97)
NYHA class					
I	389 (4.6)	119 (8.1)	23 (4.3)	37 (6.0)	59 (19.3)
II	5,919 (70.6)	1,164 (79.3)	426 (78.7)	503 (81.0)	235 (76.8)
III	2,018 (24.1)	182 (12.4)	92 (17.0)	78 (12.6)	12 (3.9)
IV	60 (0.7)	3 (0.2)	0 (0.0)	3 (0.5)	0 (0.0)
Medical history					
Hypertension	5,940 (70.7)	714 (48.6)	276 (50.9)	258 (41.5)	180 (58.8)
Diabetes	2,907 (34.6)	510 (34.7)	176 (32.5)	230 (37.0)	104 (34.0)
Atrial fibrillation	3,091 (36.8)	247 (16.8)	155 (28.6)	32 (5.2)	60 (19.6)
MI	3,634 (43.3)	503 (34.2)	150 (27.7)	262 (42.2)	91 (29.7)
Stroke	725 (8.6)	89 (6.1)	42 (7.7)	13 (2.1)	34 (11.1)
Hospitalization for HF	5,274 (62.8)	888 (60.4)	415 (76.6)	288 (46.4)	185 (60.5)
Pretrial use of ACEI	6,532 (77.8)	996 (67.8)	334 (61.6)	491 (79.1)	171 (55.9)
Pretrial use of ARB	1,892 (22.5)	474 (32.3)	207 (38.2)	132 (21.3)	135 (44.1)
Current smoker	1,208 (14.4)	967 (66.1)	152 (28.0)	50 (8.1)	39 (12.7)
Clinical features					
Dyspnoea at rest	309 (3.7)	19 (1.3)	4 (0.7)	11 (1.8)	4 (1.3)
Dyspnoea on effort	7,207 (86.0)	1,146 (78.2)	420 (77.6)	570 (91.8)	156 (51.3)
PND	399 (4.8)	40 (2.7)	8 (1.5)	27 (4.3)	5 (1.7)
Orthopnoea	608 (7.3)	53 (3.6)	5 (0.9)	26 (4.2)	22 (7.3)
JVD	818 (9.8)	83 (5.7)	18 (3.3)	62 (10.0)	3 (1.0)
Peripheral oedema	1,748 (20.8)	175 (11.9)	23 (4.3)	203 (32.7)	28 (9.2)
Treatment at randomization					
Diuretic	6,738 (80.2)	1,080 (73.5)	372 (68.6)	545 (87.8)	163 (53.3)
Digitalis	2,539 (30.2)	652 (44.4)	219 (40.4)	296 (47.7)	137 (44.8)
Beta-blocker	4,671 (55.6)	825 (56.2)	359 (66.2)	285 (45.9)	181 (59.2)
ICD	1,243 (14.8)	26 (1.8)	23 (4.2)	1 (0.2)	2 (0.7)
CRT	574 (6.8)	42 (2.9)	38 (7.0)	3 (0.5)	1 (0.3)

Values are presented as mean±standard deviation or median (interquartile range) or number (%).

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BMI = body mass index; CRT = cardiac resynchronization therapy; ICD = implantable cardioverter defibrillator; JVD = jugular venous distension; KCCQ CSS = Kansas city cardiomyopathy questionnaire clinical summary score; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NT-proBNP = N terminal pro brain natriuretic peptide; NYHA = New York Heart Association; PARADIGM-HF = Prospective comparison of Angiotensin Receptor-neprilysin inhibitor with Angiotensin converting enzyme inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure trial; PND = paroxysmal nocturnal dyspnoea; SBP = systolic blood pressure.

hypertension.<sup>52</sup>) In PARADIGM-HF, Asian patients randomized to sacubitril/valsartan overall had fewer complaints of cough compared to those randomized to enalapril, consistent with the overall findings in the total trial cohort (**Table 3**). Also, as seen in the total PARADIGM-HF population, hypotension was more common among Asians randomized to sacubitril/valsartan compared to enalapril. In Asian patients, as in the trial as a whole, patients randomized to sacubitril/valsartan had fewer adverse events leading to treatment discontinuation.

During the follow-up period, patients in Asia assigned to receive sacubitril/valsartan showed greater improvement in quality of life as indicated by the KCCQ clinical summary at 8 months compared to those receiving enalapril. Accordingly, more patients receiving enalapril had a clinically significant fall in KCCQ score at 8 months compared to sacubitril/valsartan (**Table 4**).



**Figure 2.** Event rates per 100 patient years by treatment in all patients and by Asian regions enrolled in PARADIGM-HF. HF = heart failure; PARADIGM-HF = Prospective comparison of Angiotensin Receptor-neprilysin inhibitor with Angiotensin converting enzyme inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure trial.

**Table 3.** Adverse events by treatment in all patients and by Asian regions enrolled in PARADIGM-HF

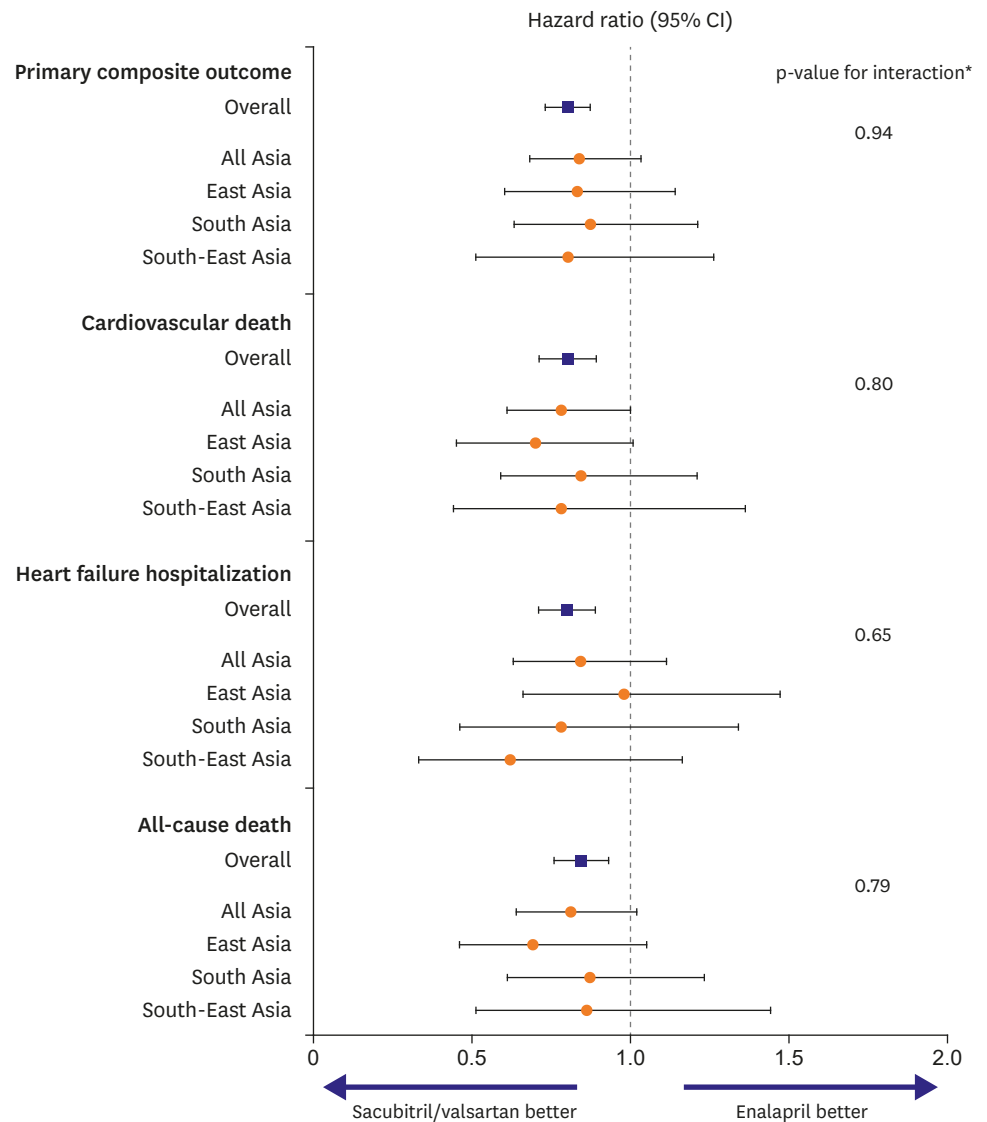
	Overall		All Asia		East Asia		South Asia		South-East Asia	
	Enalapril (n=4,212)	Sac/val (n=4,187)	Enalapril (n=731)	Sac/val (n=738)	Enalapril (n=271)	Sac/val (n=271)	Enalapril (n=307)	Sac/val (n=314)	Enalapril (n=153)	Sac/val (n=153)
Cough	601 (14.3)	474 (11.3)	211 (28.9)	156 (21.1)	68 (25.1)	50 (18.5)	83 (27.0)	57 (18.2)	60 (39.2)	49 (32.0)
Hypotension	388 (9.2)	588 (14.0)	51 (7.0)	88 (11.9)	21 (7.7)	39 (14.4)	23 (7.5)	33 (10.5)	7 (4.6)	16 (10.5)
Hyperkalaemia	455 (10.8)	395 (9.4)	57 (7.8)	49 (6.6)	14 (5.2)	17 (6.3)	38 (12.4)	28 (8.9)	5 (3.3)	4 (2.6)
Angioedema	11 (0.3)	20 (0.5)	2 (0.3)	4 (0.5)	0 (0.0)	2 (0.7)	1 (0.3)	1 (0.3)	1 (0.7)	1 (0.7)
Any AE leading to study drug discontinuation	129 (3.1)	79 (1.9)	13 (1.8)	10 (1.4)	6 (2.2)	3 (1.1)	2 (0.7)	3 (1.0)	5 (3.3)	4 (2.6)

AE = adverse event; PARADIGM-HF = Prospective comparison of Angiotensin Receptor-neprilysin inhibitor with Angiotensin converting enzyme inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure trial; Sac/val = Sacubitril/valsartan.

**Table 4.** Change in KCCQ clinical summary score by treatment in all patients and by Asian regions enrolled in PARADIGM-HF

	Overall		All Asia		East Asia		South Asia		South-East Asia	
	Enalapril (n=4,212)	Sac/val (n=4,187)	Enalapril (n=731)	Sac/val (n=738)	Enalapril (n=271)	Sac/val (n=271)	Enalapril (n=307)	Sac/val (n=314)	Enalapril (n=153)	Sac/val (n=153)
KCCQ clinical summary score rise ≥5-8 months	1,113 (26.60)	1,132 (27.20)	131 (18.10)	130 (17.70)	42 (15.60)	47 (17.40)	79 (26.20)	76 (24.30)	10 (6.50)	7 (4.60)
KCCQ clinical summary score fall ≥5-8 months	1,283 (30.70)	1,124 (27.00)	143 (19.70)	118 (16.00)	61 (22.60)	35 (13.00)	65 (21.50)	70 (22.40)	17 (11.10)	13 (8.50)

KCCQ = Kansas city cardiomyopathy questionnaire; PARADIGM-HF = Prospective comparison of Angiotensin Receptor-neprilysin inhibitor with Angiotensin converting enzyme inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure trial; Sac/val = Sacubitril/valsartan.



**Figure 3.** Treatment effects by Asian regions in PARADIGM-HF. CI = confidence interval; PARADIGM-HF = Prospective comparison of Angiotensin Receptor-neprilysin inhibitor with Angiotensin converting enzyme inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure trial. \*Interaction p value for Asia subgroups.

### IMPLEMENTATION OF SACUBITRIL/VALSARTAN IN ASIAN GUIDELINES

Guidelines for management of HF vary across different Asian regions.<sup>53)</sup> We reviewed the most up to date HF management guidelines in the Asian countries in PARADIGM-HF to see if there were any recommendations pertaining to sacubitril/valsartan. There were very few countries with up to date clinical guidelines for HF and out of those only 3 countries recommended sacubitril/valsartan in their guidelines for management of HFrEF in their patients (Table 5).

**Table 5.** Sacubitril/valsartan in failure management guidelines in Asian countries in PARADIGM-HF.

Country	Most recent year of publication	Name of issuing authority	Sacubitril/valsartan (ARNI) status
<b>East Asia</b>			
China	2018	China Heart Society <sup>60)</sup>	IB recommendation in patients who have remained symptomatic despite optimal therapy with an ACEI/ARB, a beta-blocker and an MRA.
South Korea	2017	Korean guidelines for diagnosis and management of chronic HF <sup>61)</sup>	Not included in recommendations.
Taiwan	2012	Taiwan Society of Cardiology <sup>62)</sup>	No revised guidelines.
<b>South Asia</b>			
India	2018	Cardiology Society of India <sup>63)</sup>	In patients who remain symptomatic despite optimal therapy with an ACEI, beta blocker and MRA, ARNI should be considered.
<b>South-East Asia</b>			
Malaysia	2014	Academy of Medicine of Malaysia <sup>64)</sup>	No revised guidelines.
Philippines	-	-	No revised guidelines.
Thailand	2019	HF council of Thailand <sup>65)66)</sup>	IB recommendation in patients who have remained symptomatic despite optimal therapy with an ACEI/ARB, a beta-blocker and an MRA. IIBc recommendation for ACEI/ARB naïve patients who may be able to tolerate ARNI.
Singapore	2004	Ministry of Health <sup>67)</sup>	No revised guidelines.

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; MRA = mineralocorticoid receptor antagonist; PARADIGM-HF = Prospective comparison of Angiotensin Receptor-neprilysin inhibitor with Angiotensin converting enzyme inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure trial.

## CONCLUSIONS

In PARADIGM-HF, adding a neprilysin inhibitor (sacubitril) to a renin-angiotensin system blocker (valsartan) reduced morbidity and mortality, compared to a renin-angiotensin system blocker (enalapril) alone, in ambulatory patients with chronic HFrEF. The data presented in this review support the use of sacubitril/valsartan in Asian patients with chronic, symptomatic, and ambulatory HFrEF.

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