Review Article

Sacubitril/Valsartan: A Novel Approach in the Treatment of Heart Failure with Reduced Ejection Fraction

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ABSTRACT

Heart failure is a condition in which the heart is unable to supply blood throughout the body. Heart failure [HF] is one of the main healthcare burdens in the world and is more lethal than most cancers. 50% of patients suffering with heart failure die within first 5 years of diagnosis, and 90% die within 10 years. Dyspnea [shortness of breath], Paroxysmal nocturnal dyspnea, edema, and fatigue are common symptoms. Coronary artery disease remains the leading cause of HF.

Many drugs are approved and used in practice for management of this condition, including beta blockers, diuretics, aldosterone antagonists, angiotensin converting enzyme inhibitors [ACEIs], and angiotensin receptor blockers [ARBs]. The FDA approved a drug in 2015 with the brand name Entresto — sacubitril/valsartan or LCZ696, an angiotensin receptor neprilysin inhibitor [ARNI] — for use in patients with heart failure with reduced ejection fraction [HFrEF] as a replacement to ACEIs and ARBs. The drug works through angiotensin receptor blockage via valsartan as well as neprilysin inhibition with sacubitril. This represents a new milestone in managing heart failure patients and provides a new hope for HF patients.

This was the largest-ever trial conducted for any drug in management of heart failure. The study clearly showed that sacubitril and valsartan complex can significantly reduce mortality and HF hopsitalizations ultimately helping patients stay away from hospitals.

Following the outcomes of PARADIGM-HF, the drug got a fast track approval from various regulators for HFrEF. The trial was intended to last for 36 months, but at 27 month follow-up, the results were extremely overwhelming in both the primary and secondary endpoints, therefore it was thought to be unfair to carry on further with the trial. Also, all patients in the comparator [ACEI] arm were shifted to this new drug [sacubitril/valsartan] so they could also benefit from the great advantages of this new class.

Keywords: ARNI [angiotensin receptor neprilysin inhibitor, sacubitril/valsartan], heart failure, HFrEF, ACEI [angiotensin converting enzyme inhibitor], ARBs [angiotensin receptor blockers].

Introduction

Heart failure [HF] is a leading worldwide health issue affecting more than 25 million global population. Around 60% of the global population resides in Asia[1], and two-thirds of that population lives in middle- to low-income areas.[39] Increasing prevalence of cardiovascular disease and diabetes remain the leading factors for rise in HF cases.[2, 5] Prevalence is on the rise in many countries including developed countries [Figure 2]. Moreover, the HF burden has increased, with prevalence in Asia around 1–2%, compared to 2–3% in North America and Europe.[2, 3,6] Estimated prevalence in China is around 4.5 million whereas around 2 to –4.5 million in India. Moreover, unlike the West, where HF incidence rates have been steady, the incidence of HF keeps rising in Asia, with around half a million new cases in China and up to 1.8 million in India.[3] Pakistan has similar incidence rates compared to India with cases of heart failure on the rise despite multiple drugs available.[1, 2, 3] Despite these drugs, mortality remains higher than most of the cancers [Figure 1].

Neurohormonal pathways play a central role in the pathophysiology of heart failure. The understanding that prolonged activation of Renin Angiotensin Aldosterone System and Sympathetic Nervous System [RAAS and SNS] is damaging in

heart failure underscores the foundation of therapy.[8,9,10] The significance of RAAS is strengthened by the effects of ACEIs, ARBs, and mineralocorticoid receptor antagonists [MRAs]. Similarly, the role of beta blockers supports the key role of SNS. Although the focus of therapeutic intervention is on blocking these pathways known to be harmful in heart failure, potentially helpful counter-regulatory systems are also activated in heart failure.[1]

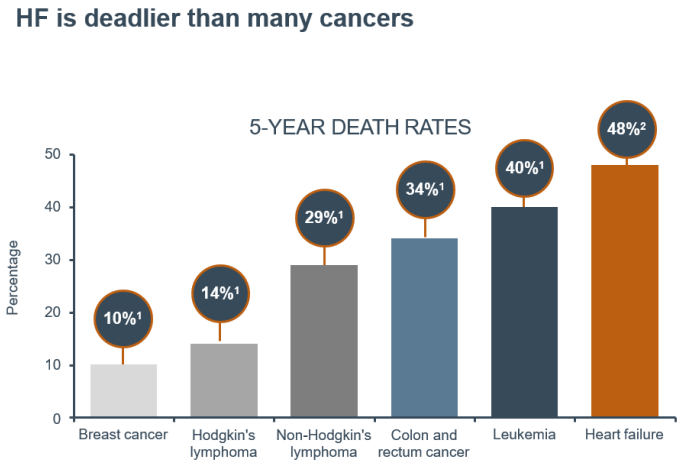

Figure 1. Five Years Mortality rate of Heart Failure compared with various cancers.

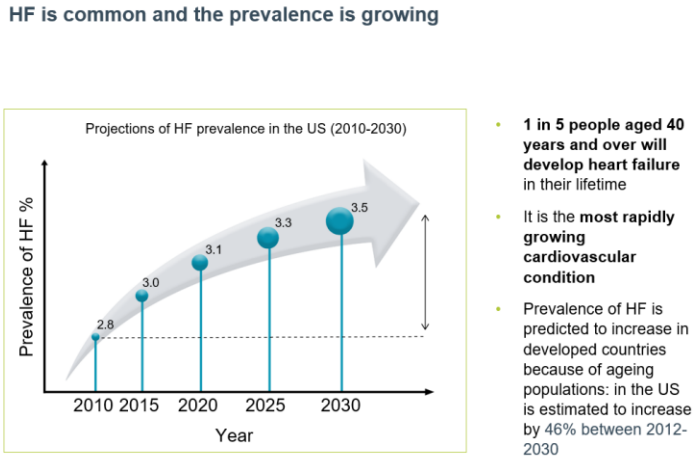

Figure 2. Prevalence and Projections of Heart Failure in US.

Types of Heart Failure

Based on ejection fraction, we categorise HF into 3 types:

1. Heart failure with a reduced ejection fraction [HFrEF] when left ventricular ejection fraction is less than 40%
2. Heart failure with midrange ejection fraction [HFmrEF] having left ventricular ejection fraction between 41 and 49%
3. Heart failure with preserved ejection fraction [HFpEF] when left ventricular ejection is above 50%

HFrEF constitutes about 50% of total HF cases[2], the breakthrough drug sacubitril/valsartan has shown great benefits in HFrEF patients with trials going on for its use in preserved ejection fraction where structural abnormalities are more profound. The most widely used diagnostic test is Echocardiograph which confirms HFrEF based on ejection fraction and other structural parameters.[28, 29]

NYHA-Based Classification of Heart Failure

The most common way to categorize HF patients is on the basis of New York Heart Association [NYHA] classification. (Table 1)

Table 1. Classification of Heart Failure on the basis of NYHA Classification.

NEW YORK HEART ASSOCIATION (NYHA) CLASSES[1]			
NYHA class I	**NYHA class II**	**NYHA class III**	**NYHA class IV**
• No limitation on physical activity • No overt symptoms	• Slight limitation on physical activities • Comfortable at rest, but ordinary physical activity causes symptoms of heart failure	• Marked limitation on physical activities • Comfortable at rest, but less than ordinary activity causes symptoms of heart failure	• Inability to carry on any activity without symptoms • Presence of symptoms even at rest

Pathophysiology and Disease Progression

Damage to cardiac myocytes leads to activation of neuro-hormonal system, leading towards detrimental effects of vasoconstriction, fibrosis, hypertrophy, sodium and water retention etc. [Figure 3]. HF patients can never be considered as stable.[2] With every acute episode of HF, patients may progress from one class to the other. More than 50% of HF deaths are sudden. This is why even apparently stable patients can take benefit from sacubitril/valsartan as the disease may progress to next stage otherwise [Figure 4].

Natriuretic Peptides and Neprilysin

Myocardial injury, which results from coronary artery disease, persistent and chronic hypertension, and myocardial infarction, often results in activation of the RAAS. This activation is compensatory initially, but over-activation of this can have detrimental effects, including vasoconstriction, fibrosis, cardiac after-load, and water and sodium retention. These effects make HF more progressive.[12, 15, 22, 39]

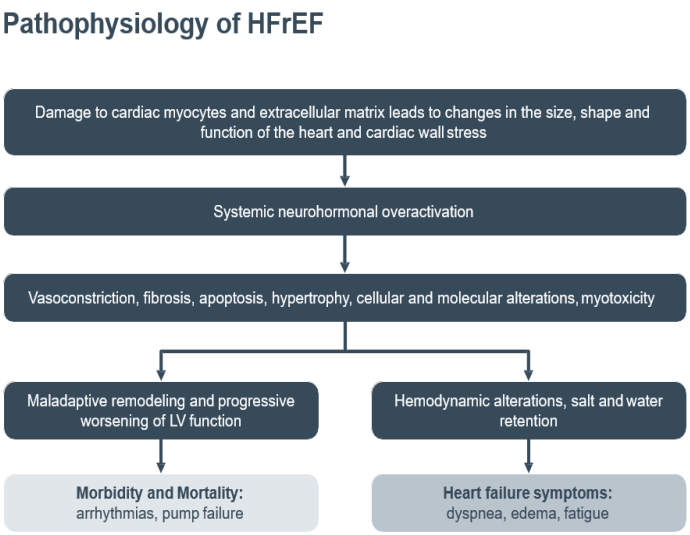

Figure 3. Pathophysiology of Heart Failure.

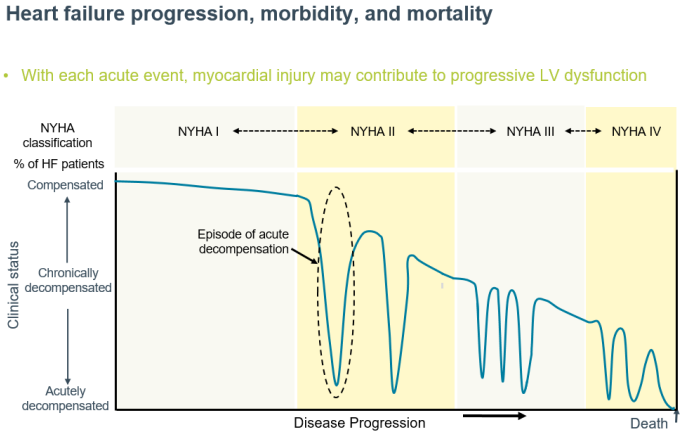

Figure 4. Disease Progression of Heart Failure.

In response to heart stress, natriuretic peptides [NPs] are released from the heart and kidneys. These natriuretic peptides help to overcome the deleterious effects of RAAS over-activation [Figure 5]. Three types of NPs have been discovered so far: ANP [A-type NP], BNP [B-type NP] and CNP [C-type NP]. The most studied and common one is BNP. Natriuresis [increased excretion of sodium through urine], antifibrosis, and vasodilation are important functions of the NP system.[21, 22]

The potential benefits of NPs led researchers to study them in detail in HF patients. One approach was the short-term IV induction of supra-physiological doses of external NP in the hospitalized patients with HF. Nevertheless, in two trials, neither nesiritide nor ularitide was able to reduce mortality or hospitalization.[25, 28, 30]

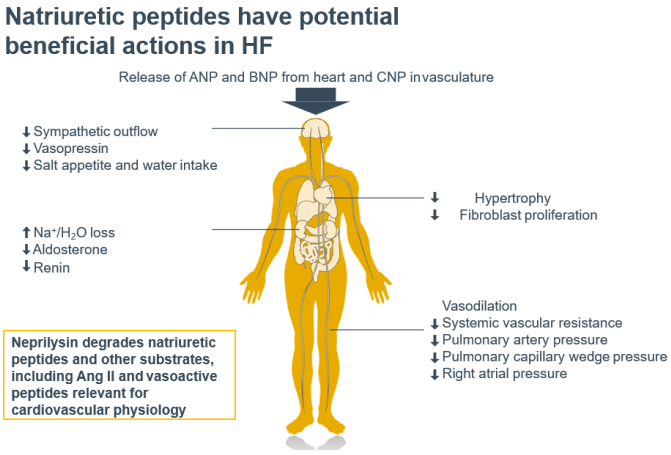

Figure 5. Natriuretic Peptides and their beneficial role in Heart Failure.

Subsequently, the successful way was to supplement the level of endogenous NPs by dropping their elimination, which takes place by two pathways. One is through an NP clearance receptor [NPRC or NPRC3] and other through neprilysin degradation.[13, 16, 22] [Figure 6].

Neprilysin Inhibition

In 1980, Roques and colleagues documented the first neprilysin inhibitor, thiorphan, in animal models with display of positive hemodynamic and hormonal responses. Past data has showed that strong neprilysin inhibition with racecadotril [formerly acetorphan] and intravenous candoxatrilat resulted in increase of diuresis and natriuresis along with a mount in circulating ANP in humans without any concurrent hazardous activation of the RAAS or sympathetic activity as seen with loop diuretics.[13, 14, 17, 25] Also, it was also shown that candoxatrilat and ecadotril reduced pulmonary capillary wedge pressure in patients with HF.[5, 16,18]

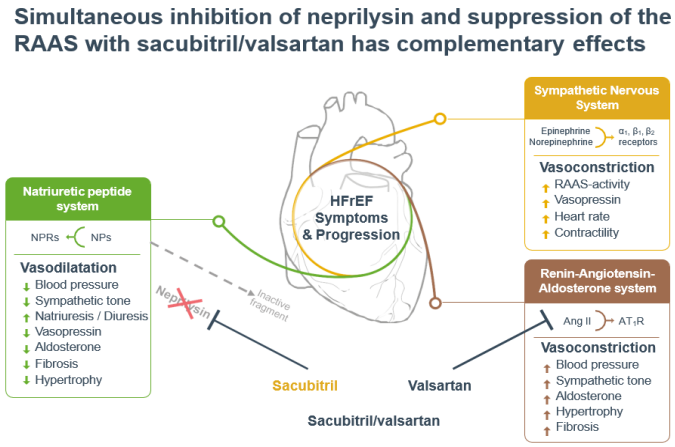

Figure 6. Neprilysin inhibition complements RAAS blockage.

PARADIGM-HF Trial

PARADIGM-HF studied the efficacy and safety of adding a neprilysin inhibitor to a RAAS blocker, compared with a renin-angiotensin system blocker [and other standard therapy] alone.[8,11,22] It was a geographically diverse trial with 985 sites [Figure 7]. Run in phase subjected all patients to Enalapril 10 mg BID followed by Sacubitril/Valsartan 100 mg BID which was up titrated to target dose of 200 mg BID. After which, the study was divided into two arms, one arm taking Enalapril 10 mg BID and the other arm taking Sacubitril/Valsartan 200 mg BID [Figure 8].

Geographically Diverse Trial in Patients with HFrEF

8,442 PATIENTS WERE RANDOMIZED AT 985 SITES

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; BID = twice daily; HFrEF = heart failure with reduced ejection fraction; TDD = total daily dose. McMurray JJ, et al. Eur J Heart Fail. 2013;15:1062–73; McMurray JJ, et al. N Engl J Med. 2014;371:993-1004; McMurray JJ, et al. Eur J Heart Fail. 2014;16:817–25

Clinical Efficacy of Sacubitril/Valsartan in PARADIGM-HF

Sacubitril/valsartan demonstrated clinical and mortality benefits. The drug reduced CV mortality by 20%, HF hospitalization by 21% and all cause mortality by 16%. All three reductions were significant and had a major impact on the success of the trial. [1,22, 23] [Figure 9].

Figure 7. Geographic diversity of PARADIGM-HF Trial

Study Design of PARADIGM-HF

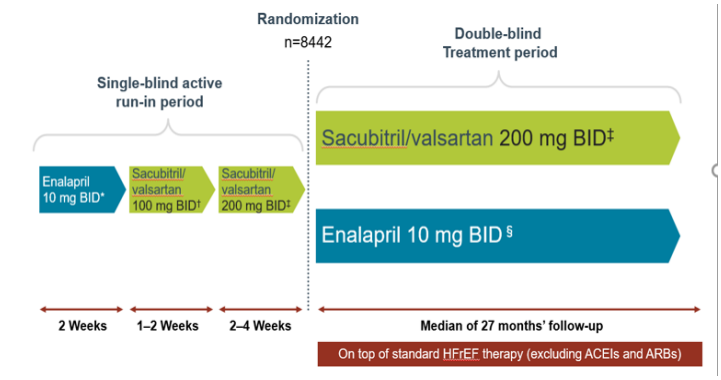

Figure 8. Study design of PARADIGM-HF Trial.

Comparable and significant reductions were seen in the two main types of CV deaths which are sudden death and due to HF worsening.[22, 23, 25,39]

It was concluded that for a thousand patients switched to sacubitril/valsartan from enalapril, there would be fourth six lesser composite endpoint events, twentyseven lesser first heart failure hospitalizations, thirty one fewer CV deaths and twenty eight fewer deaths from any cause.[33]

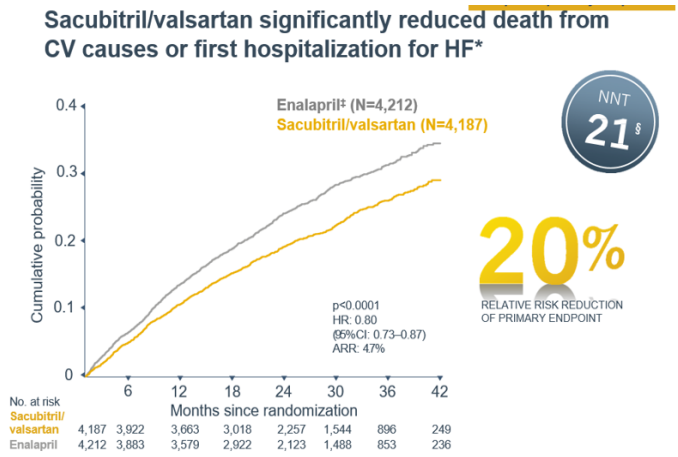

Figure 9. Mortality and Hospitalization benefits of Sacubitril/Valsartan as compared to Enalapril.

Summary of Baseline Characteristics

Table II: Baseline characteristics of Patients in PARADIGM-HF Trial.

Characteristic	Sacubitril/valsartan (n=4,187)	Enalapril (n=4,212)
Age, years	63.8 ± 11.5	63.8 ± 11.3
Women, n (%)	879 (21.0)	953 (22.6)
Region, n (%)		
North America	310 (7.4)	292 (6.9)
Latin America	713 (17.0)	720 (17.1)
Western Europe and other‡	1026 (24.5)	1025 (24.3)
Central Europe	1393 (33.3)	1433 (34.0)
Asia-Pacific	745 (17.8)	742 (17.6)
Ischemic cardiomyopathy, n (%)	2,506 (59.9)	2,530 (60.1)
LV ejection fraction, %	29.6 ± 6.1	29.4 ± 6.3
NYHA functional class, n (%)		
II	2,998 (71.6)	2,921 (69.3)
III	969 (23.1)	1,049 (24.9)
SBP, mmHg	122 ± 15	121 ± 15
Heart rate, beats/min	72 ± 12	73 ± 12
NT-proBNP, pg/mL (IQR)	1,631 (885–3,154)	1,594 (886–3,305)
BNP, pg/mL (IQR)	255 (155–474)	251 (153–465)

Safety and Tolerability of Sacubitril/Valsartan in PARADIGM-HF

Although events of hypotension were reported to be slightly more in sacubitril/valsartan group as compared to enalapril group, still, the discontinuation due to this was rarely observed [Table III]. There was no major difference in incidence of angioedema while events of hperkalemia, renal dysfunction and cough were lesser in the sacubitril/valsartan group PARADIGM-HF.[7, 31,32 33]

Table III: Comparison of safety events in both arms of PARADIGM-HF Trial.

Prospectively defined safety events — PARADIGM-HF

Event, n (%)	Sacubitril/valsartan (n=4,187)	Enalapril (n=4,212)	p-value
Hypotension			
Symptomatic	588 (14.0)	388 (9.2)	<0.001
Symptomatic with SBP <90 mmHg	112 (2.7)	59 (1.4)	<0.001
Elevated serum creatinine			
≥2.5 mg/dL	139 (3.3)	188 (4.5)	0.007
≥3.0 mg/dL	63 (1.5)	83 (2.0)	0.10
Elevated serum potassium			
>5.5 mmol/L	674 (16.1)	727 (17.3)	0.15
>6.0 mmol/L	181 (4.3)	236 (5.6)	0.007
Cough	474 (11.3)	601 (14.3)	<0.001
Angioedema (adjudicated by a blinded expert committee)			
No treatment or use of antihistamines only	10 (0.2)	5 (0.1)	0.19
Catecholamines or glucocorticoids without hospitalization	6 (0.1)	4 (0.1)	0.52
Hospitalized without airway compromise	3 (0.1)	1 (<0.1)	0.31
Airway compromise	0	0	---

Regulatory Approval and Statistical Robustness of Results

The overwhelmingly outcomes and promising prospects of PARADIGM-HF speedily resulted in getting a positive signal from major regulatory entities. In order to win a regulatory endorsement, the new drug needs to demonstrate its efficacy and safety in at least two trials having a p value of <0.05.

On grounds of certain meta analysis, we can confidently argue in favour of sacubitril/valsartan as having superiority over traditional HF medicines. The safety is also established in various trials is comparable to enalapril.[23, 26, 27]

PARADIGM-HF demanded patients to be tolerant of a dose of an ACE inhibitor or an ARB equivalent to enalapril 10 mg/day prior to enrolment. However, several following trials suggest that

sacubitril and valsartan can be used in ARB or ACE naive patients. This fact has been recommended based on the findings of Transition and Titration trials.[21]

Asians in the PARADIGM-HF Trial

Around fifteen hundred Asians were a part of PARADIGM-HF trial making it an inclusive trial representing diverse patient population.[8]

Region wise detailed analysis shows that patients from Asian the trial had better BMIs, were younger and responded better to the experimental drug. [Table IV]. These findings were largely replicated in the Asian sub-groups that we analysed for this review. In an earlier analysis by Kristensen et al.[20] Asian patients had more probability of receiving digoxin and less chances of getting other drugs and device treatments at the time of randomization.[20, 23]

Conclusion

PARADIGM-HF was a landmark trial which changed the landscape of HF management. Previously ACE inhibitors were considered as a gold standard in the management of heart failure but with the findings of the trial, it was clearly demonstrated that neprilysin inhibition and RAAS blockade provides

Table IV: Asians in PARADIGM HF Trial.

	Overall		All Asia		East Asia		South Asia		South-East Asia	
Age [years]	[n=8,399]		[n=1,469]		[n=542]		[n=621]		[n=306]	
Sex [female]	63.8±11.4		57.8±11.9		59.7±11.9		57.1±11.7		56.0±11.8	
SBP [mmHg]	1,832	[21.8]	287	[19.5]	96	[17.7]	134	[21.6]	57	[18.6]
Heart rate [bpm]	121±15		117±15		116±14.6		117±13		119±17	
BMI [kg/m2]	72±12		75±11		73±12		77±9		75±13	
Serum creatinine [mg/dL]	28.1±5.5		24.3±4.1		25.0±3.8		23.5±3.9		24.6±4.8	
Clinical features of HF	1.12±0.3		1.06±0.3		1.05±0.3		1.03±0.3		1.15±0.3	
Ischemic cardiomyopathy										
LVEF [%]	5,036	[60.0]	855	[58.2]	209	[38.6]	449	[72.3]	197	[64.4]
Median NT-proBNP [pg/mL]	29.5±6.2		28.1±5.9		29.5±5.3		27.5±5.8		27.0±6.6	
Median KCCQ CSS	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]	
NYHA class	80	[63–92]	89	[79–96]	91	[82–97]	87	[77–96]	89	[71–97]
I										
II	389	[4.6]	119	[8.1]	23	[4.3]	37	[6.0]	59	[19.3]
III	5,919	[70.6]	1,164	[79.3]	426	[78.7]	503	[81.0]	235	[76.8]
IV	2,018	[24.1]	182	[12.4]	92	[17.0]	78	[12.6]	12	[3.9]
Medical history	60	[0.7]	3	[0.2]	0	[0.0]	3	[0.5]	0	[0.0]
Hypertension										
Diabetes	5,940	[70.7]	714	[48.6]	276	[50.9]	258	[41.5]	180	[58.8]
Atrial fibrillation	2,907	[34.6]	510	[34.7]	176	[32.5]	230	[37.0]	104	[34.0]
MI	3,091	[36.8]	247	[16.8]	155	[28.6]	32	[5.2]	60	[19.6]
Stroke	3,634	[43.3]	503	[34.2]	150	[27.7]	262	[42.2]	91	[29.7]
Hospitalization for HF	725	[8.6]	89	[6.1]	42	[7.7]	13	[2.1]	34	[11.1]
Pretrial use of ACEI	5,274	[62.8]	888	[60.4]	415	[76.6]	288	[46.4]	185	[60.5]
Pretrial use of ARB	6,532	[77.8]	996	[67.8]	334	[61.6]	491	[79.1]	171	[55.9]
Current smoker	1,892	[22.5]	474	[32.3]	207	[38.2]	132	[21.3]	135	[44.1]
Clinical features	1,208	[14.4]	967	[14.0]	152	[28.0]	50	[8.1]	39	[12.7]
Dyspnoea at rest										
Dyspnoea on effort	309	[3.7]	19	[1.3]	4	[0.7]	11	[1.8]	4	[1.3]
PND	7,207	[86.0]	1,146	[78.2]	420	[77.6]	570	[91.8]	156	[51.3]
Orthopnoea	399	[4.8]	40	[2.7]	8	[1.5]	27	[4.3]	5	[1.7]
JVD	608	[7.3]	53	[3.6]	5	[0.9]	26	[4.2]	22	[7.3]
Peripheral oedema	818	[9.8]	83	[5.7]	18	[3.3]	62	[10.0]	3	[1.0]
Treatment at randomization	1,748	[20.8]	175	[11.9]	23	[4.3]	203	[32.7]	28	[9.2]
Diuretic										
Digitalis	6,738	[80.2]	1,080	[73.5]	372	[68.6]	545	[87.8]	163	[53.3]
Beta-blocker	2,539	[30.2]	652	[44.4]	219	[40.4]	296	[47.7]	137	[44.8]
ICD	4,671	[55.6]	825	[56.2]	359	[66.2]	285	[45.9]	181	[59.2]
CRT	1,243	[14.8]	26	[1.8]	23	[4.2]	1	[0.2]	2	[0.7]
	574	[6.8]	42	[2.9]	38	[7.0]	3	[0.5]	1	[0.3]

significant reductions in mortality and HF hospitalizations. The safety and tolerability profile of ARNi was comparable to that of ACE inhibitors.

Moreover, follow-up trials and post-hoc analysis done with the drug showed that ARNi can be given in ACE or ARB naive patients. Also, better glycemic and HDL controls were seen in patients using ARNi. Asians responded rally well in the PARADIGM trial and had a better response to the drug.

PROVE-HF and its positive outcome has enhanced the understanding of how ARNI can help cardiac remodelling which ultimately improves the ejection fraction in patients. Similarly TRANSITION and PIONEER-HF trials conducted on ARNI have expanded its use in hospitalized patients.

ESC Consensus paper released in 2019 supports and recommends use of ARNI [Sacubitril/Valsartan] as first line treatment option and according to the release, if thought suitable, it is not required to start the patients on ACEI or other HF drugs prior to shifting to ARNI. More trials and sub-analysis on ARNI are paving the way to make it the drug of choice and first line treatment option in HFrEF patients. With the use of this drug, 1 out of every 5 HFrEF patients can be saved from mortality with great improvements in their quality of life including greater walking distances without experiencing shortness of breath. This new class will go down as one of the major breakthroughs in cardiovascular field.

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