Am J Cardiovasc Dis 2021;11(6):734-742
www.AJCD.us /ISSN:2160-200X/AJCD0134423

Original Article

SAcubitril/valsartan versus ramipril in patients with ST-segment Elevation Myocardial Infarction and cardiogenic SHOCK (SAVE-SHOCK): a pilot randomized controlled trial

Ahmed Rezq[1,2], Marwan Saad[1,3], Mostafa El Nozahi[1]

[1]Department of Cardiology, Ain Shams University, Cairo, Egypt; [2]Department of Cardiology, Dar Al Fouad Hospital, Cairo, Egypt; [3]Cardiovascular Institute, Warren Alpert Medical School at Brown University, Providence, RI, USA

Received April 18, 2021; Accepted May 25, 2021; Epub December 15, 2021; Published December 30, 2021

Abstract: Objectives: To evaluate the safety and efficacy of sacubitril/valsartan versus ramipril in patients with STEMI and cardiogenic shock. Methods: Patients who received primary percutaneous coronary intervention (PPCI) for STEMI complicated with cardiogenic shock were randomized 1:1 to sacubitril/valsartan versus ramipril after clinical stabilization. The primary outcome was major adverse cardiac events (MACE) at 30 days and 6 months. Secondary in-hospital clinical outcomes included recurrent shock, new or re-initiation of vasoactive medications, and acute kidney injury (AKI). All-cause death, cardiac death, hospitalization due to heart failure (HF), myocardial infarction (MI), and stroke were examined at 30 days and 6 months. Study ID 016-01-2018. Results: 100 patients with STEMI and cardiogenic shock were included (mean age 54.7±10.3 years, 87% men). Initiation of sacubitril/valsartan and ramipril occurred at 38.18±18.44 versus 39.0±21.03 hours after stabilization, respectively. The primary outcome was similar between both groups at 30 days and 6 months. No difference in in-hospital or 30-day clinical outcomes was observed. However, at 6 months, patients in the sacubitril/valsartan arm suffered less hospitalization with HF (18% vs 38%, P=0.044) compared with patients in the ramipril arm. Other clinical outcomes at 6 months were similar between both groups. Conclusions: Sacubitril/valsartan in patients with STEMI and cardiogenic shock may be associated with improved clinical outcome at 6 months compared with ramipril. Larger randomized controlled trials with longer follow-up are recommended.

Keywords: Sacubitril/valsartan, Entresto®, STEMI, cardiogenic shock

Introduction

Cardiogenic shock is the major cause of in-hospital mortality in patients with acute myocardial infarction (MI). Incidence of cardiogenic shock as a complication of MI ranges from 5 to 15% [1-8], even though some of this data originate from studies before the era of primary percutaneous coronary intervention (PPCI) [1, 2]. Despite the standard use of PPCI in patients with ST-segment elevation myocardial infarction (STEMI), and the advanced technology in hemodynamic support when needed in these cases, in-hospital mortality associated with STEMI and cardiogenic shock remains high [6-11].

Hypotension after STEMI activates the RAS-aldosterone system that leads to excess angiotensin II production which enhances norepinehrine release. Both angiotensin II and NE stimulates myocyte hypertrophy and ANP secretion [12-14].

Sacubitril/valsartan is an angiotensin receptor-neprilysin inhibitor (ARNI) that showed superiority to enalapril in chronic as well as acute heart failure with reduced ejection fraction (HFrEF) in the PARADIGM-HF and PIONEER-HF trials, respectively [15-18]. Sacubitril/valsartan had demonstrated potential role in reducing heart failure hospitalizations at 6 months in patients with STEMI [19]. However, the safety and efficacy associated with early use of sacubitril/valsartan in patients who are clinically stable after STEMI and cardiogenic shock is unknown. In this study, we aimed at examining the role of sacubitril/valsartan versus conventional angio-

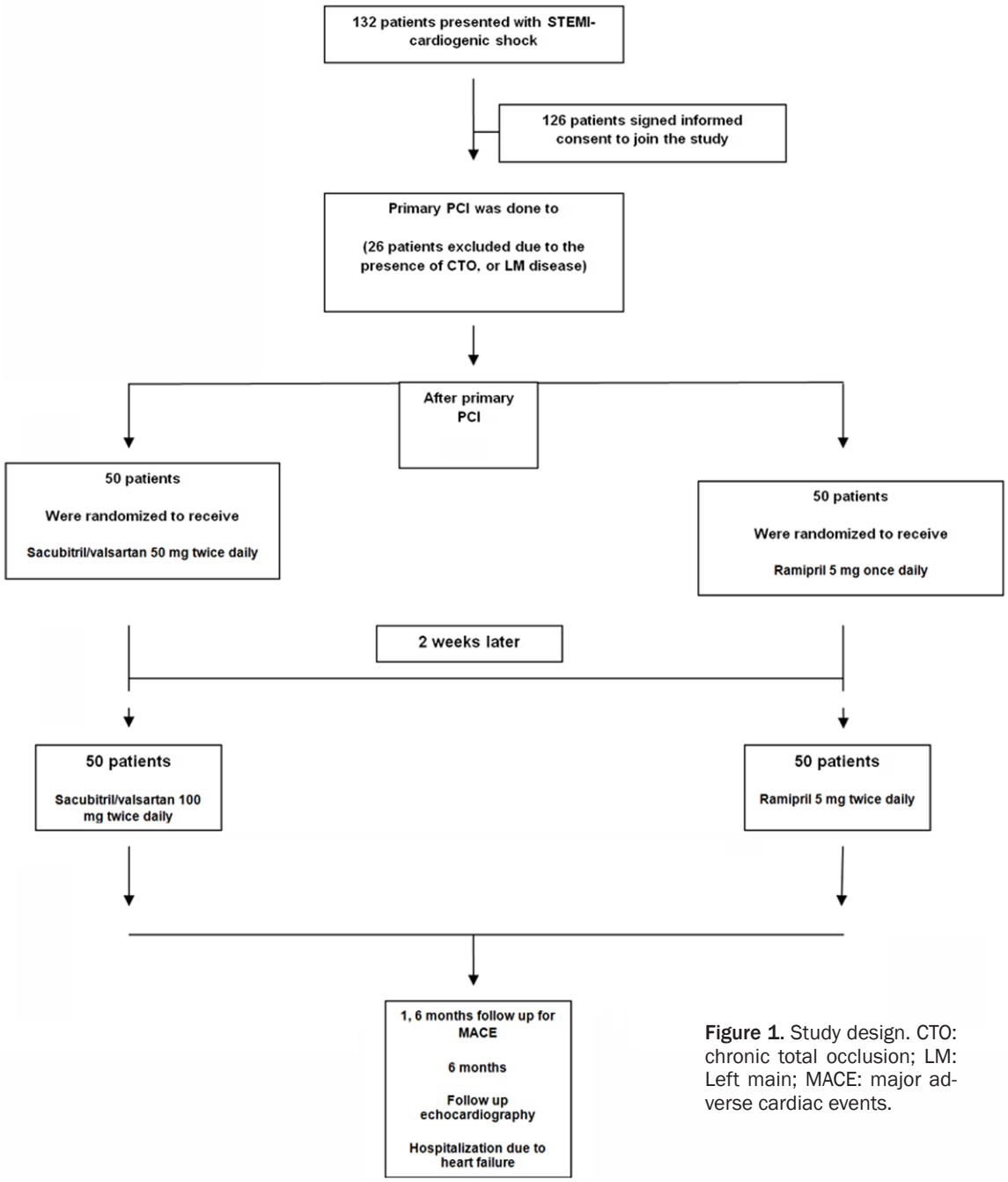

Figure 1. Study design. CTO: chronic total occlusion; LM: Left main; MACE: major adverse cardiac events.

tensin converting enzyme inhibitor in patients with STEMI and cardiogenic shock.

Methods

Study design and population

This is a prospective, double blinded, randomized study conducted in three tertiary centers in Egypt (Ain Shams University, Dar Al Fouad Hospitals, and Mabaret Al Asafra Hospital). Patients were enrolled from February 2018 to January 2020. Patients between 18 and 90 years of age, who presented with STEMI and cardiogenic shock within 12 hours of the onset of chest pain, were included (**Figure 1**). Cardiogenic shock was defined as systolic blood pressure (SBP) less than 90 mmHg for more than 30 minutes, or the use of pharmacological/mechanical support to maintain SBP above 90 mmHg, together with evidence of end organ damage including urine output of less

than 30 ml/hour, cold extremities, or serum lactate of more than 2.0 mmol/L [20]. We excluded patients with a) known coronary artery disease (e.g., prior MI, PCI, or coronary artery bypass grafting [CABG]), b) known LV systolic dysfunction, c) bleeding tendency, or d) chronic kidney disease. Patients who developed acute kidney injury in the setting of cardiogenic were not started on either medication until improvement of kidney function.

Before PPCI, all patients were pretreated with oral aspirin 300 mg plus Ticagrelor 180 mg or clopidogrel 600 mg as a loading dose followed by maintenance dose. The use of adjunctive medical or mechanical therapy (e.g., vasoactive medications, glycoprotein IIb/IIIa inhibitors, aspiration thrombectomy, or mechanical circulatory support) was left to operators' decision. Written informed consent was provided by all participants before randomization.

Treatment, randomization, and blinding

After primary PCI, patients were randomized 1:1 to receive sacubitril/valsartan (starting dose of 50 mg twice daily) vs ramipril (starting dose of 5 mg once daily). Physicians were blinded to the treatment groups. Doses were up titrated to sacubitril/valsartan 100 mg twice daily versus ramipril 5 mg twice daily after 2 weeks if tolerated (**Figure 1**). Time for starting either medication was at least 24 hours after hemodynamic stabilization from cardiogenic shock. All patients continued on aspirin and P2Y12 inhibitor (ticagrelor or clopidogrel). Other guideline-directed medical therapy was initiated after STEMI as well.

Outcomes

The primary outcome was major adverse cardiac events (MACE) at 30 days and 6 months. MACE was defined as composite endpoint of cardiac death, MI, and hospitalization due to HF. Secondary safety clinical outcomes included recurrent shock, new or re-initiation of vasoactive medications, significant hyperkalemia (i.e., >5.5 mmol/L), and acute kidney injury (AKI). AKI was defined as a rise in the creatinine concentration of ≥0.5 mg/dL [≥44 μmol/L] and/or a decline in the estimated GFR of ≥25% [8]. Secondary efficacy clinical outcomes included all-cause death, cardiac death, hospitalization due to heart failure (HF), myocardial infarction (MI), and stroke were examined at 30 days and 6 months [21].

Follow up

Patients were clinically evaluated in outpatient clinic visits one week after discharge, at 30 days, and 6 months. Echocardiographic evaluation at 6 months was performed according to the standard guidelines [22]. Physicians were blinded to the treatment groups.

Statistical analysis

Categorical variables were presented as numbers and percentages, and compared using chi-square tests, or Fisher's exact tests as appropriate, while continuous data were reported as means and standard deviations and compared using Student's t-test. A two-sided *P* value of less than 0.05 was considered significant. Kaplan Meier survival curve was obtained from log rank analysis. Statistical analyses were done using SPSS 18.0 software (SPSS Inc., Chicago, Illinois).

Ethical committee approval

This study was performed according to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the ethical committees at all centers (study ID 016-01-2018).

Patient and public involvement

Neither patients nor any public authority was involved in the study design or participated in any data collection or analysis. Patients were aware of the study after proper explanation of the protocol.

Results

During the study period, PPCI was performed to 100 patients who presented with STEMI complicated by cardiogenic shock. Mean age was 53.12±9.08 vs 55.5±12.5 years in the sacubitril/valsartan versus ramipril, respectively. Baseline demographic data are presented in **Table 1**. The severity of CAD, door-to-balloon time, and use of GPI or thrombus aspiration were similar in both groups. All patients received drug-eluting stents. The use of inotropic drugs (82% vs 84%) and mechanical circulatory

Table 1. Baseline clinical characteristics

	Sacubitril/valsartan (N=50 patients)	Ramipril (N=50 patients)	*P*-Value
Age, years (mean ± SD)	53.12±9.08	55.5±12.5	0.281
Male gender, %	35.0	38.0	0.653
Diabetes, %	30.0	33.0	0.679
Insulin therapy, %	12.0	6.0	0.192
Hypertension, %	33.0	31.0	0.835
Dyslipidemia, %	43.0	47.0	0.318
Smoking, %	33.0	37.0	0.513
Family history of coronary artery disease, %	14.0	23.0	0.097
Renal impairment, %	0	2.0	0.495
SBP	57.4±11.6	55.6±10.5	0.418
DBP	31.2±9.8	31.0±7.4	0.908
Creatinine (mg/dL)	1.15±0.40	1.25±0.33	0.164
Creatinine CL (ml/min/m^2)	73.8±22.9	67.5±20.2	0.147

Table 2. Procedural data of both groups

	Sacubitril/valsartan (N=50 patients)	Ramipril (N=50 patients)	*P*-Value
Duration from onset of pain till first medical contact, hours (mean ± SD)	3.8±2.8	4.2±3.2	0.293
Door-to-balloon time, minutes (mean ± SD)	50.2±3.4	49.8±5.1	0.861
Inotropes	41 (82.0%)	42 (84.0%)	0.790
Peak CK-Mb	280.5±136.4	307.5±131.2	0.317
Mechanical Ventilation	10 (20%)	8 (16%)	0.795
Intra-aortic balloon	11 (22%)	9 (18%)	0.795
Infarct-related artery (IRA), (%)			
Left anterior descending artery	34 (68%)	31 (62%)	0.837
Right coronary artery	11 (22%)	12 (24%)	0.810
Left circumflex artery	3 (6%)	4 (8%)	1.000
Diagonal artery, Obtuse marginal	2 (4%)	3 (6%)	1.000
Baseline TIMI flow (IRA)	0.2±0.5	0.2±0.4	0.595
Thrombus burden (IRA)	4.5±1.1	4.7±0.8	0.332
Mean stent diameter, mm (mean ± SD)	3.2±0.3	3.6±0.4	0.247
Mean stent length, mm (mean ± SD)	20.2±3.1	21.4±3.4	0.061
Mean number of stents (mean ± SD)	2.5±1.0	2.5±0.7	0.735
GP IIb/IIIa inhibitors intraprocedural, (%)	5 (10%)	6 (12%)	1.000

GP= Glycoprotein; SD= standard deviation; TIMI= Thrombolysis In Myocardial Infarction; IRA= infarct related artery; NIRA= Non-infarct related artery.

support (20% vs 16%) were similar in patients in the sacubitril/valsartan versus ramipril arms, respectively. Initiation of Sacubitril/Valsartan versus ramipril started 38.18±18.44 hours versus 39.0±21.03 hours after hemodynamic stabilization (P=0.93). Procedural details are presented in **Table 2**, in-hospital course in **Table 3**.

Outcomes

The primary outcome of MACE was similar between both groups at 30 days (2% vs 8%) and 6 months (24% vs 42%). Secondary safety clinical outcomes were similar between both groups. No patients in either group had recurrent shock or significant hypotension after starting the medication. At 30 days and 6 months, the clinical outcomes of all-cause death, MI, stroke were similar. Hospitalization for HF was similar at 30 days, however, at 6 months, patients in the sacubitril/valsartan arm suffered less hospitalization with HF (18% vs 38%, P=0.044) compared with patients in the ramipril arm.

Table 3. In-hospital course

	Sacubitril/ valsartan (N=50 patients)	Ramipril (N=50 patients)	*P*-Value
In-hospital			
Duration of mechanical ventilation, hours (mean ± SD)	9.4±2.5	10.8±2.4	0.230
Duration of IV inotropes, hours (mean ± SD)	8.8±7.1	9.2±5.7	0.783
Duration of intra-aortic balloon	9.2±2.6	11.8±3.2	0.096
Initiation of ACE vs Sac/Val after extubation and withdrawal of IV supports, hours (mean ± SD)	38.18±18.44	39.0±21.03	0.929
Initiation of beta blockers after extubation and withdrawal of IV supports, hours (mean ± SD)	25.09±8.4	25.5±7.6	0.915
Life threatening arrhythmias	18 (36%)	15 (30%)	0.671

Table 4. Clinical efficacy outcomes

	Sacubitril/ valsartan (N=50 patients)	Ramipril (N=50 patients)	*P*-Value
In-hospital			
MACE, %	6 (12%)	5 (10%)	1.000
All-cause death, %	0 (0%)	0 (0%)	
Cardiac death, %	3 (6%)	2 (4%)	1.000
Recurrent myocardial infarction, %	0 (0%)	0 (0%)	
Stroke, %	2 (4%)	1 (2%)	1.000
Bleeding, %	1 (2%)	2 (4%)	1.000
CIN	2 (4%)	3 (6%)	1.000
Renal replacement therapy	0 (0%)	1 (2%)	1.000
30 days follow up			
MACE, %	1 (2%)	4 (8%)	0.362
HF hospitalization, %	0 (0%)	2 (4%)	0.495
All-cause death, %	0 (0%)	0 (0%)	
Cardiac death, %	0 (0%)	0 (0%)	
Myocardial infarction, %	1 (2%)	2 (4%)	1.000
Stroke, %	0 (0%)	0 (0%)	
6 months follow up			
MACE, %	12 (24%)	21 (42%)	0.088
HF hospitalization, %	9 (18%)	19 (38%)	0.044
All-cause death, %	1 (2%)	0 (0%)	0.317
Cardiac death, %	1 (2%)	0 (0%)	1.000
Myocardial infarction, %	1 (2%)	2 (4%)	1.000
Stroke, %	0.0	1 (2%)	1.000

HF= heart failure; MACE= major adverse cardiac events.

Outcomes are summarized in **Table 4**. Though Kaplan Meier survival curve didn't show a significant difference, the events rate was less in the sacubitril/valsartan group (**Figure 2**).

*Echocardiographic data (**Table 5**)*

Echocardiographic assessment in-hospital showed an ejection fraction of 29.8±6.9% versus 29.6±5.8% (P=0.22) in the study group versus ramipril group. At 6 months, a significant improvement in the LV ejection fraction in the sacubitril/valsartan versus the ramipril group, 35.2±6.1% versus 32.4±5.8%, P=0.002 respectively.

Discussion

In the current study, we show important findings. The use of sacubitril/valsartan after clinical stabilization in patients with STEMI and cardiogenic shock was safe and associated with reduced HF hospitalization and improved systolic function at 6-month follow up compared with ramipril.

Cardiogenic shock is a life-threatening condition that complicates 5% to 10% of cases of acute MI and is the major cause of sudden cardiac death after MI. STEMI is associated with a 2-fold augmented risk for development of cardiogenic shock compared to NSTEMI [23]. Survivors of MI-associated cardiogenic shock have an 18.6% risk of 30-day readmission with an average of 10 days after discharge. The risk of readmission is to some extent less among patients with STEMI versus NSTEMI. The main reasons are congestive heart failure and new myocardial infarction [24]. Once patients have received initial therapy to remove congestion and improve dyspnea

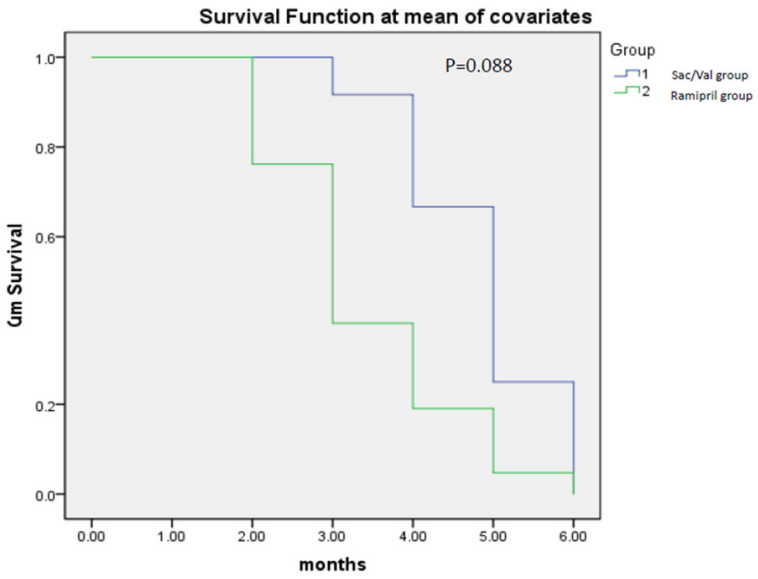

Figure 2. KM curve showing less events rates in the Sacubitril/Valsartan group and better survival compared to ramipril group though not statistically significant.

then the focus of treatment should switch to disease-modifying drugs which improve mortality and long-term outcomes such as hospitalization for heart failure, and recurrent myocardial infarction. Heart failure activates the renin-angiotensin system which increases aldosterone, and blood pressure, promotes vasoconstriction, fibrosis, and left ventricular hypertrophy. The majority of therapies such as ACE inhibitors, beta blockers, and mineralocorticoid receptor antagonists work by blocking this pathway.

This study is a multi-center, prospective, double blinded, randomized study conducted at 3 tertiary centers in Egypt. The study presents encouraging preliminary data regarding the safety of early administration of sacubitril/valsartan within few days after stabilization of patients who presented with STEMI and cardiogenic shock. The plausible cause of its beneficial effect is improving cardiac remodeling and LV function, and subsequently reducing the incidence of heart failure hospitalization. However, it is important to note that initiation of such medications in this sick population should be performed during hospitalization with involvement of heart team, intensivists, as well as nephrologists in case of renal dysfunction, and close monitoring should be performed to avoid recurrence of hemodynamic instability.

Hypotension in the setting of myocardial infarction activates the RAS-aldosterone axis that leads to excess catecholamine production by adrenal medulla, as well as the secretion of natriuretic peptides [12]. Activation of beta-1 adrenoreceptors in the juxtaglomerular apparatus enhances renin release, which promotes the release of angiotensin II. Increased angiotensin II induces the presynaptic release of norepinephrine (NE) and blocks its reuptake, in addition to catecholamine synthesis, and potentiates the postsynaptic action of NE [13]. Both angiotensin II and NE may provoke ET-1 production, which stimulates myocyte hypertrophy and ANP secretion [14].

No solid, sufficient data is on hand concerning safety and efficiency of Angiotensin-Neprilysin Inhibition in the setting of STEMI complicated with cardiogenic shock. Inhibition of RAAS which is the cornerstone regulating the myocardial remodeling after MI seems beneficial and considered a cornerstone therapy in the routine protocols for the STEMI patients after primary PCI. The dual effect of inhibiting both angiotensin II production as well as neprilysin inhibition may have an additive value reducing LV dilatation and consequent reduction of the LV systolic functions after STEMI compared to the usual ACE inhibitor-only therapies.

According to our data, the main determinants whether to start Sacubitril/Valsartan or not after patient stabilization were a) the hemodynamic stability of the patient, regarding his blood pressure, perfusion, as well as the absence of any life-threatening arrhythmias, and b) eGFR, renal functions and absence of hyperkalemia. These were main factors that should guide the decision whether to initiate the treatment or not. It seems clear that early initiation markedly improved the LV systolic functions and dimensions. Accordingly, this

Table 5. Left ventricular echocardiographic data of both groups

	Sacubitril/valsartan (N=50 patients)	Ramipril (N=50 patients)	*P*-Value
In-hospital			
LV end diastolic dimension, mm (mean ± SD)	57.67±6.1	57.43±6.0	0.781
LV end systolic dimension, mm (mean ± SD)	41.6±4.0	41.3±5.5	0.060
LV ejection fraction, % (mean ± SD)	29.8±6.9	29.6±5.8	0.220
Six months			
LV end diastolic dimension, mm (mean ± SD)	54.6±4.7	56.7±5.4	0.005
LV end systolic dimension, mm (mean ± SD)	38.8±4.9	40.7±5.7	0.011
LV ejection fraction, % (mean ± SD)	35.2±6.1	32.4±5.8	0.001

LV= left ventricle; SD= standard deviation.

improved the short-term outcomes, and minimized hospitalization due to heart failure within 6 months. Though it didn't have a remarkable effect on survival, but this might be attributed to the small cohort number of our study, as the KM survival curve showed relatively better survival and fewer events in the study group.

Though the maximal, long term treatment effect of ARNI remains uncertain, however, their short-term benefits in patients with acute decompensated heart failure are well proven. This group improves fluid retention, as well as New York Heart Association (NYHA) class which might relate to their long-term effects on hospitalization and mortality. Adding NI to ARBs definitely improved cardiac remodeling especially in patients with high NT-proBNP compared to the standard ACEIs. But the safety of using these drugs after acute decompensation still needs thorough evaluation. The PIONEER-HF (Comparison Of Sacubitril/valsartaN Versus Enalapril on Effect on nt-pRo-bnp in Patients Stabilized From an Acute Heart Failure Episode) study may help to clarify this issue [16].

Our study is limited by including a small cohort of patients; hence, it is hard to generalize our results, and to exclude type 1 errors.

Conclusion

Sacubitril/valsartan in patients with STEMI and cardiogenic shock may be associated with improved clinical outcome at 6 months compared with ramipril. Larger randomized controlled trials with longer follow-up are recommended.

Acknowledgements

The study was funded by Departments of Cardiology at Ain Shams University, Dar Al Fouad hospital, and Mabaret Al Asafra hospital.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Ahmed Rezq, Ain Shams University, Abbassia Square, Cairo, Egypt. Tel: +20-2-01112000889; E-mail: dr.ahmedrezq@yahoo.com

References

[1] Hochman JS, Buller CE, Sleeper LA, Boland J, Dzavik V, Sanborn TA, Godfrey E, White HD, Lim J and LeJemtel T. Cardiogenic shock complicating acute myocardial infarction-etiologies, management and outcome: a report from the SHOCK trial registry. Should we emergently revascularize Occluded Coronaries for cardiogenic shock. J Am Coll Cardiol 2000; 36 Suppl: 1063-1070.

[2] Goldberg RJ, Spencer FA, Gore JM, Lessard D and Yarzebski J. Thirty-year trends (1975 to 2005) in the magnitude of, management of, and hospital death rates associated with cardiogenic shock in patients with acute myocardial infarction: a population-based perspective. Circulation 2009; 119: 1211-1219.

[3] Redfors B, Angerås O, Råmunddal T, Dworeck C, Haraldsson I, Ioanes D, Petursson P, Libungan B, Odenstedt J, Stewart J, Lodin E, Wahlin M, Albertsson P, Matejka G and Omerovic E. 17-year trends in incidence and prognosis of cardiogenic shock in patients with acute myocardial infarction in western Sweden. Int J Cardiol 2015; 185: 256-262.

[4] Goldberg RJ, Makam RC, Yarzebski J, McManus DD, Lessard D and Gore JM. Decade long trends (2001-2011) in the incidence and hospital death rates associated with the in-hospital development of cardiogenic shock after

acute myocardial infarction. Circ Cardiovasc Qual Outcomes 2016; 9; 117-125.

[5] Aissaoui N, Puymirat E, Tabone X, Charbonnier B, Schiele F, Lefèvre T, Durand E, Blanchard D, Simon T, Cambou JP and Danchin N. Improved outcome of cardiogenic shock at the acute stage of myocardial infarction: a report from the USIK 1995, USIC 2000, and FAST-MI French nationwide registries. Eur Heart J 2012; 33: 2535-2543.

[6] Harjola VP, Lassus J, Sionis A, Køber L, Tarvasmäki T, Spinar J, Parissis J, Banaszewski M, Silva-Cardoso J, Carubelli V, Di Somma S, Tolppanen H, Zeymer U, Thiele H, Nieminen MS and Mebazaa A; CardShock Study Investigators; GREAT network. Clinical picture and risk prediction of short-term mortality in cardiogenic shock. Eur J Heart Fail 2015; 17: 501-509.

[7] Puymirat E, Fagon JY, Aegerter P, Diehl JL, Monnier A, Hauw-Berlemont C, Boissier F, Chatellier G, Guidet B, Danchin N and Aissaoui N; Collège des Utilisateurs de Bases de données en Réanimation (CUB-Réa Group [Intensive Care Database User Group]). Cardiogenic shock in intensive care units: evolution of prevalence, patient profile, management and outcomes, 1997-2012. Eur J Heart Fail 2017; 19: 192-200.

[8] Sánchez-Salado JC, Burgos V, Ariza-Solé A, Sionis A, Canteli A, Bernal JL, Fernández C, Castrillo C, Ruiz-Lera M, López-de-Sá E, Lidón RM, Worner F, Martínez-Sellés M, Segovia J, Viana-Tejedor A, Lorente V, Alegre O, Llaó I, González-Costello J, Manito N, Cequier Á, Bueno H and Elola J. Trends in cardiogenic shock management and prognostic impact of type of treating center. Rev Esp Cardiol (Engl Ed) 2019; 73: 546-553.

[9] Mebazaa A, Combes A, van Diepen S, Hollinger A, Katz JN, Landoni G, Hajjar LA, Lassus J, Lebreton G, Montalescot G, Park JJ, Price S, Sionis A, Yannopolos D, Harjola VP, Levy B and Thiele H. Management of cardiogenic shock complicating myocardial infarction. Intensive Care Med 2018; 44: 760-773.

[10] De Luca L, Olivari Z, Farina A, Gonzini L, Lucci D, Di Chiara A, Casella G, Chiarella F, Boccanelli A, Di Pasquale G, De Servi S, Bovenzi FM, Gulizia MM and Savonitto S. Temporal trends in the epidemiology, management, and outcome of patients with cardiogenic shock complicating acute coronary syndromes. Eur J Heart Fail 2015; 17: 1124-1132.

[11] Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, Richardt G, Hennersdorf M, Empen K, Fuernau G, Desch S, Eitel I, Hambrecht R, Fuhrmann J, Böhm M, Ebelt H, Schneider S, Schuler G and Werdan K; IABP-SHOCK II Trial Investigators. Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med 2012; 367: 1287-1296.

[12] Ju H, Zhao S, Tappia PS, Panagia V and Dixon IM. Expression of Gq alpha and PLC-beta in scar and border tissue in heart failure due to myocardial infarction. Circulation 1998; 97: 892-829.

[13] Ball SG. The sympathetic nervous system and converting enzyme inhibition. J Cardiovasc Pharmacol 1989; 13 Suppl 3: S17-S21.

[14] Levin ER, Gardner DG and Samson WK. Mechanisms of disease: natriuretic peptide. N Engl J Med 1998; 339: 321-328.

[15] Parikh KS, Lippmann SJ, Greiner M, Heidenreich PA, Yancy CW, Fonarow GC and Hernandez AF. Scope of sacubitril/valsartan eligibility after heart failure hospitalization: findings from the GWTG-HF Registry (get with the guidelines-heart failure). Circulation 2017; 135: 2077-80.

[16] Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, Rocha R and Braunwald E; PIONEER-HF Investigators. Angiotensin-neprilysin inhibition in acute decompensated heart failure. N Engl J Med 2019; 380: 539-48.

[17] Hollenberg SM, Warner Stevenson L, Ahmad T, Amin VJ, Bozkurt B, Butler J, Davis LL, Drazner MH, Kirkpatrick JN, Peterson PN, Reed BN, Roy CL and Storrow AB. 2019 ACC expert consensus decision pathway on risk assessment, management, and clinical trajectory of patients hospitalized with heart failure: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2019; 74: 1966-2011.

[18] Seferovic PM, Ponikowski P, Anker SD, Bauersachs J, Chioncel O, Cleland JGF, de Boer RA, Drexel H, Ben Gal T, Hill L, Jaarsma T, Jankowska EA, Anker MS, Lainscak M, Lewis BS, McDonagh T, Metra M, Milicic D, Mullens W, Piepoli MF, Rosano G, Ruschitzka F, Volterrani M, Voors AA, Filippatos G and Coats AJS. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail 2019; 21: 1169-86.

[19] Rezq A, Saad M and El Nozahi M. Comparison of the efficacy and safety of sacubitril/valsartan versus ramipril in patients with st-segment elevation myocardial infarction. Am J Cardiol 2021; 143: 7-13.

[20] van Diepen S, Katz JN, Albert NM, Henry TD, Jacobs AK, Kapur NK, Kilic A, Menon V, Ohman EM, Sweitzer NK, Thiele H, Washam JB and Cohen MG; American Heart Association Council

on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Quality of Care and Outcomes Research; and Mission: Lifeline. Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. Circulation 2017; 136: e232-e268.

[21] Hicks KA, Tcheng JE, Bozkurt B, Chaitman BR, Cutlip DE, Farb A, Fonarow GC, Jacobs JP, Jaff MR, Lichtman JH, Limacher MC, Mahaffey KW, Mehran R, Nissen SE, Smith EE and Targum SL. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American Heart Association Task Force on clinical data standards (writing committee to develop cardiovascular endpoints data standards). J Am Coll Cardiol 2015; 66: 403-69.

[22] Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, Tsang W and Voigt JU. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr 2015; 28: 1-39, e14.

[23] Kolte D, Khera S, Aronow WS, Mujib M, Palaniswamy C, Sule S, Jain D, Gotsis W, Ahmed A, Frishman WH and Fonarow GC. Trends in incidence, management, and outcomes of cardiogenic shock complicating STelevation myocardial infarction in the United States. J Am Heart Assoc 2014; 3: e000590.

[24] Mahmoud AN, Elgendy IY, Mojadidi MK, Wayangankar SA, Bavry AA, Anderson RD, Jneid H and Pepine CJ. Prevalence, causes, and predictors of 30 day readmissions following hospitalization with acute myocardial infarction complicated by cardiogenic shock: findings from the 2013-2014 National Readmissions Database. J Am Heart Assoc 2018; 7: e008235.