Comparison of the Efficacy and Safety of Sacubitril/Valsartan versus Ramipril in Patients With ST-Segment Elevation Myocardial Infarction

Ahmed Rezq, MD PhD[a,b,*], Marwan Saad, MD, PhD[a,c], and Mostafa El Nozahi, MD PhD[a]

The role of sacubitril and/or valsartan in patient with heart failure (HF) is established. Whether sacubitril and/or valsartan plays a role in improving outcomes in patients after ST-segment elevation myocardial infarction (STEMI) is unknown. The current study aims to comparing the efficacy and safety of sacubitril and/or valsartan versus ramipril in post-STEMI patients. Patients presenting with STEMI were randomized to receive either sacubitril and/or valsartan or ramipril after primary percutaneous coronary intervention. The main efficacy endpoint was major adverse cardiac events (MACE) at 30 days and 6 months, defined as a composite of cardiac death, myocardial infarction, and HF hospitalizations. Multiple secondary clinical safety and efficacy endpoints were examined. A total of 200 patients were randomized from January 2018 to March 2019, mean age 54.5±10.4, 87% men, 75% presented with anterior wall STEMI. Baseline clinical and echocardiographic characteristics were comparable between groups. The primary endpoint of MACE was similar with sacubitril/valsartan versus ramipril at 30 days (p = 0.18); however, at 6 months, sacubitril/valsartan was associated with significant reduction of MACE (p = 0.005), mainly driven by reduction in HF hospitalizations (18% vs 36%, OR 0.40, 95% 0.22 to 0.75; p = 0.004). At 6 months, LV ejection fraction was higher with sacubitril/valsartan (46.8±12.5% vs 42.09±13.8%; p = 0.012), with improved LV remodelling (LV end diastolic dimension 50.6±3.9 mm vs 53.2±2.7 mm, p = 0.047; and LV end systolic dimension 36.1±3.4 mm versus 39.9±6.3 mm, p = 0.001) compared with ramipril. No difference in other efficacy or safety clinical endpoints was observed. In conclusion, early initiation of sacubitril/valsartan may offer clinical benefit and improvement in myocardial remodelling in post-STEMI patients. **(Am J Cardiol 2021;143:7−13)**

Despite the efficiency of primary percutaneous coronary intervention in restoring coronary blood flow in patients with ST-elevation myocardial infarction,[1−3] myocardial dysfunction in those patients is not uncommon. Myocardial dysfunction can occur as a result of microvascular dysfunction with reduced myocardial perfusion, delayed reperfusion, or large territory of infarction, leading to adverse myocardial remodelling, poor ejection fraction, and increased mortality.[4,5] Sacubitril and/or valsartan is an angiotensin receptor-neprilysin inhibitor (ARNI) that showed superiority to enalapril in patients with chronic stable heart failure and reduced ejection fraction (HFrEF) in the PARADIGM-HF study,[6,7] and was replicated in patients with acute decompensated HFrEF in the PIONEER-HF trial.[8] Recent expert consensus documents extended the benefit of sacubitril and/or valsartan from chronic HFrEF to include patients with acute decompensation.[9,10] However, the role of sacubitril and/or valsartan in post- ST-segment elevation myocardial infarction (STEMI) patients has not been yet studied, and whether its early use after STEMI can improve clinical outcomes remains unknown. In the current study we sought to compare the safety and efficacy of sacubitril and/or valsartan versus a conventional angiotensin-receptor inhibitor (ramipril) in patients who underwent successful primary PCI for STEMI.

Methods

This is a 2-centre, prospective, double blinded, randomized study conducted at 2 tertiary centres in Cairo, Egypt, namely Ain Shams University and Dar Al Fouad Hospitals. Patients' recruitment started in January 2018 and ended in March 2019. We included patients with age between 18 and 90 years who presented with STEMI within 24 hours after symptom onset irrespective of signs of ongoing ischemia. Exclusion criteria included patients with: (1) hemodynamic instability, (2) prior thrombolysis, (3) bleeding gastric ulcer or severe gastritis in the last 6 months, (4) advanced liver disease, (5) bleeding diathesis, (6) previous PCI, (7) prior MI, (8) previous coronary artery bypass grafting (CABG), (9) established LV systolic dysfunction or known ischemic cardiomyopathy. The study was approved by the ethical

[a]Department of cardiology, Ain Shams University, Abbassia Square, Cairo, Egypt; [b]Department of cardiology, Dar Al Fouad Hospital, Cairo, Egypt; and [c]Cardiovascular Institute, Warren Alpert Medical School at Brown University, Providence, Rhode Island. Manuscript received October 25, 2020; revised manuscript received and accepted December 7, 2020.

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*Corresponding author: Tel.: +2 01112000889

E-mail address: dr.ahmedrezq@yahoo.com (A. Rezq).

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committees at both centres. All patients provided written informed consent before randomization.

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.

After primary PCI for STEMI, eligible patients were assigned in a 1:1 ratio to either sacubitril/valsartan or ramipril group, using a computer-generated list of random numbers. Both patients and physicians were blinded to the treatment groups. The initial dose of sacubitril/valsartan was 50 mg twice daily orally that was increased to 100 mg twice daily orally after 2 weeks if tolerated, while ramipril was started as 5 mg once daily orally and was increased to 5 mg twice daily 2 weeks later, if tolerated (Figure 1). All patients received aspirin, $P2Y_{12}$ inhibitor (ticagrelor or clopidogrel), beta blockers as well as statins. Antiplatelet therapy was started prior to primary PCI. All other medications were started immediately after primary PCI if hemodynamics permit. If not, reassessment of the patient's vital signs was performed continuously to determine the appropriate time of starting the medications. A detailed list of medications in each group is summarized in Supplemental Table 1.

The main efficacy endpoint was major adverse cardiac event (MACE) at 30 days and 6 months. MACE was defined as composite endpoint of cardiac death, myocardial infarction (MI), and HF hospitalization. Secondary efficacy endpoints included all-cause death, cardiac death, HF hospitalization, myocardial infarction, and stroke at 30 days and 6 months. Left ventricular (LV) echocardiographic parameters were reported at 6 months, including LV end-systolic dimensions, LV end-diastolic dimensions, and ejection fraction. Clinical endpoints were defined according to the American College of Cardiology and/or American Heart Association guidelines.[11] Echocardiographic measurements were performed according to the current guidelines.[12]

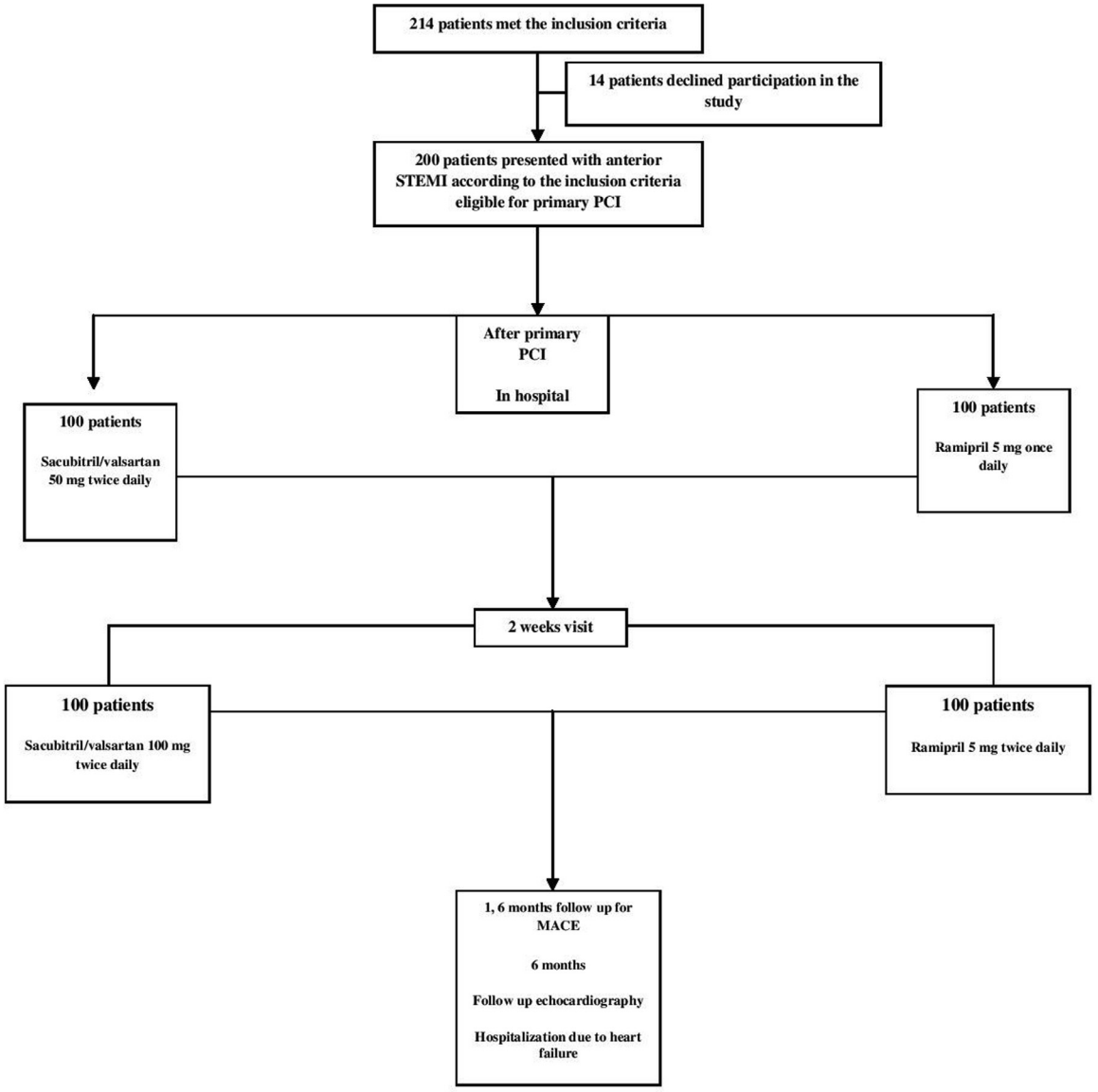


Figure 1. Study design.

The safety endpoints included symptomatic hypotension, significant hyperkalaemia, worsening renal function, and angioedema. Symptomatic hypotension was defined as clinical symptoms of low cardiac output with systolic blood pressure ≤ 90 mm Hg and/or diastolic blood pressure ≤ 60 mm Hg. Significant hyperkalaemia was defined as potassium level ≥ 5.5 mmol/L. Worsening renal function was defined as an increase in the serum creatinine concentration of ≥ 0.5 mg per decilitre [≥ 44 μmol per litre] and/or a decrease in the estimated glomerular filtration rate of ≥ 25% as previously defined.[8] All outcome definitions were adjudicated by a clinical event committee of 3 independent and blinded experts.

All patients were followed in clinic at 1 week, 2 weeks, 30 days, and 6 months by physicians who are blinded to the treatment. Laboratory workup was obtained at all visits. Echocardiography was performed at 6 months.

Our analysis was based on an intention-to-treat principle. Categorical variables were reported as numbers and percentages, and continuous data as means and standard deviations. Fixed effect odds ratios and 95% confidence intervals were calculated. Continuous variables were compared by Student's *t*-test, while categorical variables were compared by chi-square tests, or Fisher's exact tests as appropriate. Two-sided p values were calculated and considered significant if less than 0.05. Log rank analysis was performed to obtain the Kaplan Meier survival curve. Statistical analyses were performed with SPSS 18.0 (SPSS Inc., Chicago, Illinois).

Results

From January 2018 through March 2019, a total of 214 patients met our eligibility criteria. Fourteen patients declined participation in the study, and a total of 200 patients were randomized. Patients in the ramipril group was slightly older than those in the sacubitril/valsartan group (57±11.6 years vs 52±9.2 years). Both groups were homogenous in other baseline characteristics (Table 1).

There was no significant difference in the door-to-balloon time in sacubitril/valsartan versus ramipril groups (44.6±22.7 versus 53.7±39.1 mins, p = 0.28). Left anterior descending artery was the infarct-related artery in the majority of cases in both groups (72% versus 78% in sacubitril and/or valsartan versus ramipril groups, respectively, p = 0.41). Thrombolysis In Myocardial Infarction (TIMI) flow was similar in both groups (0.2±0.5 versus 0.2±0.4 for sacubitril and/or valsartan and ramipril groups, respectively, p = 0.59). Table 2 summarizes procedural data for both groups.

Five patients in the sacubitril/valsartan versus 7 patients in the ramipril group had significant non-culprit stenoses that required intervention during the index hospitalization (p = 0.76). No mechanical or electrical complications were encountered in either groups.

The primary outcome of MACE was similar with sacubitril/valsartan versus ramipril at 30 days (1% versus 4%; OR: 0.29, 95% CI 0.05 to 1.73, p = 0.18). At 6 months, sacubitril/valsartan was associated with significant reduction in MACE (20% vs 38%, OR 0.42, 95% CI 0.23 to 0.78; p = 0.005) compared with ramipril. Kaplan Meier survival curve showed a significant difference in favour of the study group (Figure 2).

At 30 days, there were no death or stroke in either group. HF hospitalization (0% vs 2%) and MI (1% vs 2%) were similar with sacubitril/valsartan and ramipril, respectively. At 6 months, there was a significant reduction in HF hospitalization with sacubitril/valsartan (18% vs 36%, OR 0.40, 95% 0.22 to 0.75; p = 0.004) compared with ramipril. Only one cardiac death was observed in the sacubitril and/or valsartan group, and no stroke was observed in either groups at 6 months. MI was similar between both groups (1% vs 2%).

In-hospital LV dimensions and function were similar between both groups (LVEDD: 55.4±4.3 vs 54.4±5.8 mm; p = 0.63; LVESD: 39.8±5.1 versus 40.8±6.2 mm; p = 0.49), and LV EF 39.49±14.6% versus 41.73±15.4%; p = 0.29) with sacubitril and/or valsartan and ramipril, respectively. At 6 months, sacubitril and/or valsartan was associated with improvement in LV myocardial remodelling and reduction in LVEDD (50.6±3.9 versus 53.2±2.7 mm; p = 0.047) and LVESD (36.1±3.4 vs 39.9±6.3 mm; p = 0.001) with improvement in LV EF (46.8±12.5% vs 42.09±13.8%; p = 0.012) compared with ramipril.

Table 1
Baseline clinical characteristics

Variable	Sacubitril/valsartan (N=100 patients)	Ramipril (N=100 patients)	p Value
Age, (years) (mean±SD)	52 ± 9.2	57 ± 11.6	0.05
Men	86%	88%	0.83
Body mass index(BMI) (kg/m^2)	28.7± 4.3	29.2± 3.5	0.783
Heart rate (bpm)	91.5±11.9	91.0±12.7	0.929
Serum Creatinine (mg/dl)	1.15±0.40	1.25±0.33	0.164
Peak CPK level (IU/L)	1977.8±1799.6	2224.6±2197.5	0.636
Peak CPK-MB level (IU/L)	298.8±187.7	370.8±218.9	0.176
Diabetes mellitus	40%	34%	0.46
Insulin therapy	24%	12%	0.04
Hypertension	34%	38%	0.65
Systolic blood pressure	97.4±11.6	95.6±10.5	0.418
Dyslipidemia	86%	94%	0.09
Smoking	66%	74%	0.28
Family history of coronary artery disease	8%	12%	0.48
Renal impairment	0	4%	0.12

Table 2
Procedural data of both groups

Variable	Sacubitril/valsartan (N=100 patients)	Ramipril (N=100 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
Infarct-related coronary artery			
Left anterior descending	72%	78%	0.414
Right	20%	16%	0.581
Left circumflex	0	4%	0.121
Diagonal	4%	0	0.121
Obtuse marginal	0	2%	0.497
Posterior descending	4%	0	0.121
Other	26%	16%	0.181
Site of coronary stenosis			
Ostial	8%	0	0.007
Proximal third	72%	68%	0.644
Mid third	18%	32%	0.033
Distal third	2%	0	0.497
Baseline TIMI flow	0.2 ± 0.5	0.2 ± 0.4	0.595
Thrombus burden	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
GP IIb/IIIa inhibitors intraprocedural	0	0	
Stent post dilatation	3%	4%	0.93[a]

[a] GP= Glycoprotein; SD= standard deviation; TIMI = Thrombolysis In Myocardial Infarction

No safety adverse events (symptomatic hypotension, significant hyperkalaemia, worsening renal function, or angioedema) were observed with either groups. Maximum doses prespecified by the trial were tolerated by all patients in both arms.

Discussion

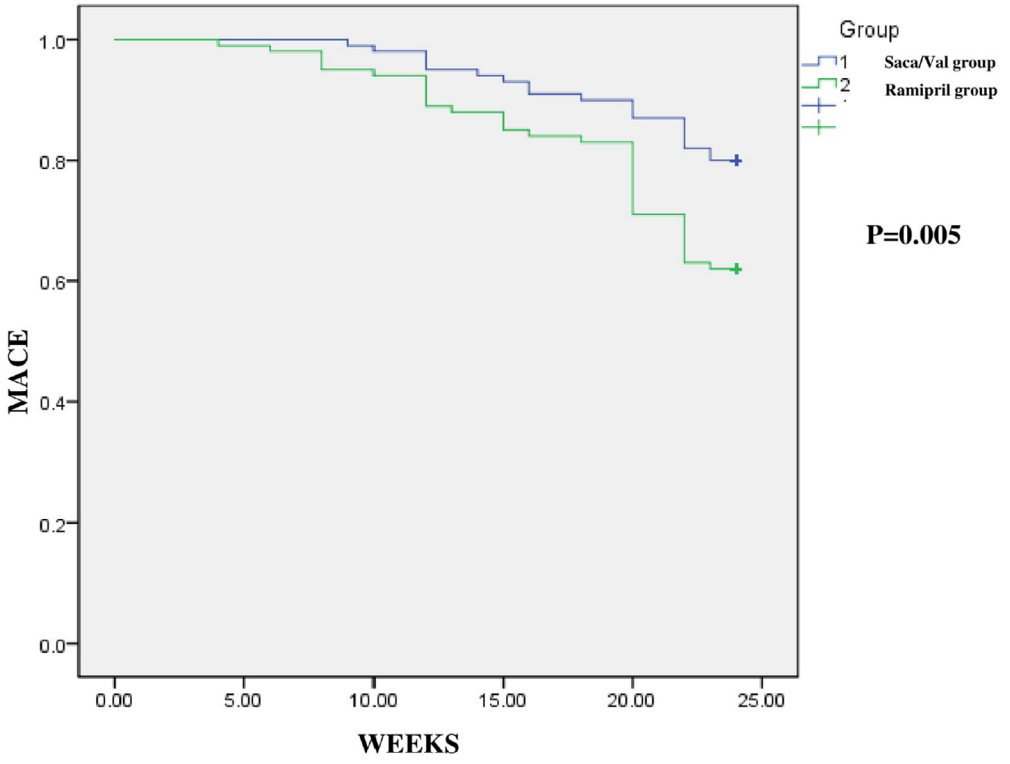
The SAVE-STEMI trial is a randomized, active controlled, double blinded, 2-center study that was performed to examine the role of early initiation of sacubitril/valsartan after primary PCI for STEMI patients, in comparison to a conventional ACE inhibitor (ramipril). The most important findings of our study were: (1) sacubitril and/or valsartan was associated with reduced MACE (defined as a composite of cardiac death, MI, and HF hospitalization at 6 months, mainly driven by significant reduction in HF hospitalization compared with ramipril; (2) sacubitril and/or valsartan was associated with improvement in LV adverse myocardial remodelling after 6 months compared with ramipril. No safety adverse events were observed with either group.

Myocardial injury initiates a pattern of remodelling including the infarcted border area and remote noninfarcted myocardium. Remodelling includes myocyte hypertrophy and alterations in ventricular architecture to distribute the increased wall stress more evenly as the extracellular matrix creates a collagen scar to stabilize the distending forces and hinder more deformation.[13] Myocyte hypertrophy is initiated by neurohormonal activation, myocardial stretch, the activation of the local tissue renin angiotensin aldosterone system (RAAS), and paracrine and/or autocrine factors.[14]

The RAAS system is the main determinant of the pathophysiology of heart failure (HF) and its inhibition is essential to improve outcomes in patients with HFrEF. Many randomized controlled trials have shown that blockade of RAAS improves morbidity and mortality in those patients.[15–17] The natriuretic peptide system counter regulates the injurious effects of the upregulation of RAAS that occurs in HFrEF, prevents the secretion of arginine and vasopressin and regulates the autonomic nervous system in ways that are presumably advantageous in this condition.[18]

Early attempts at inhibiting neprilysin using an oral (racecodotril) [19] and intravenous (candoxatrilat) [20] were successful in helping natriuresis and elevating urinary excretion of atrial natriuretic peptide (ANP). However, a study of chronic use of the oral prodrug candoxatril showed that the preliminary drop in blood pressure was not sustained. This could be attributed to the finding that neprilysin also breaks down angiotensin II.[21–23] Therefore, inhibiting neprilysin alone, while raising natriuretic peptides levels, also increases angiotensin II levels (and other substrates for neprilysin such as endothelin, vasopressin, bradykinin, etc.) potentially counteracting the effects of the former peptides. One strategy to combat these unwanted effects of lone neprilysin inhibition is with blockade of the renin-angiotensin system with an angiotensin receptor antagonist along with the effects in potentiating the natriuretic peptide system.

The Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF) was performed to examine whether 97 mg/103 mg twice daily of sacubitril and/or valsartan was superior to enalapril 10 mg twice daily in reducing the primary end point of CV death or HF hospitalization.[6] The trial was terminated early, based on the suggestion of the Data Monitoring Committee, due to a constant and noteworthy drop in the risk of the primary end points (cardiac death or HF hospitalization) and in cardiac



Numbers at risk

Sacubitril/Valsartan	100	100	98	93	87	80
Ramipril	100	100	94	85	71	62

Figure 2. KM survival curve of the main outcome of the study, major adverse cardiac events (MACE).

mortality in the sacubitril and/or valsartan group compared with the enalapril group. By the conclusion of the trial, there was a 20% relative risk reduction in the primary end points, as well as a 16% reduction in all-cause mortality. The 2 major modes of cardiac death, sudden death and death from worsening HF, were equally and significantly reduced.

More recently, the Angiotensin−Neprilysin Inhibition in Acute Decompensated Heart Failure (PIONEER-HF) trial compared sacubitril/valsartan versus enalapril in patients with acute decompensated HFrEF.[8] Sacubitril/valsartan was associated with significant reduction in the level of NT-proBNP concentration compared with enalapril therapy, as early as 1 week after initiation, with no significant difference in adverse events.

No data is available regarding the safety and efficacy of Angiotensin−Neprilysin Inhibition post STEMI. According to our study, early initiation of sacubitril/valsartan seemed to improve the short-term outcomes post MI, by reducing HF hospitalization and LV remodelling. It seems that the standard regimens for the STEMI patients after primary PCI may benefit from an inhibition of RAAS which is one of the cornerstones regulating the myocardial remodelling after MI. The dual effect of inhibiting both angiotensin II receptors in addition to neprilysin may have a role in preventing post MI LV dilatation and subsequent reduction of systolic function compared with the standard ACE inhibitor-only regimens.

Among the reasons why sacubitril and/or valsartan proved effective in our study is the high prevalence of anterior wall STEMI, which is likely to be the cohort that would benefit the most from prevention of myocardial remodelling. It is encouraging to see absence of significant difference in adverse events between both groups. This was also observed in the PIONEER-HF trial.

The current study is the first pilot trial, to our knowledge, to examine the role of sacubitril/valsartan in post-STEMI patients. However, our study does not come without limitations. It is a small-sized pilot trial with low event rates and hence, type 1 errors cannot be entirely excluded. Also, our study is not a multinational study, and hence outcomes may not be generalized to all post-STEMI patients worldwide. An ongoing larger randomized trial with longer follow (Prospective ARNI vs ACE Inhibitor Trial to DetermIne Superiority in Reducing Heart Failure Events After MI; PARADISE-MI) is eagerly awaited to confirm our results.[24]

In conclusion, early initiation of sacubitril/valsartan after STEMI may offer a role in reducing MACE and HF hospitalization in comparison to ACE inhibitors. Although this will add a new indication for this new class of medications needs to be further confirmed on larger scale cohort of patients with longer follow up to ensure safety and efficacy.

Authors Contribution

All 3 authors are responsible for designing the study, enrolment of patients, follow up as well as collecting and analysing data.

Study Registration

Local registration at Ain Shams University and Dar Al Fouad. Study ID 001-12-2017

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.12.037.

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