Objective: To compare the safety and efficacy of valsartan/sacubitril (angiotensin receptor neprilysin inhibitor [ARNI]) against enalapril (angiotensin-converting enzyme inhibitor [ACEI]) in patients with acute heart failure at 6-month follow-up. Methods: In this prospective, single centre, and observational study conducted between September 2017 and February 2020 in India, patients with acute decompensated heart failure with reduced ejection fraction (<40%) were included. Patients were divided in two groups: valsartan/sacubitril (ARNI) group and enalapril (ACEI). Patients were followed up for at least 6 months after administration of first dose and were evaluated for safety, efficacy, and tolerability of target drug. Student's independent t-test was employed for comparing continuous variables. Chi-square test or Fisher's exact test, whichever appropriate, was applied for comparing categorical variables. Results: A total of 200 patients were included in the present study,100 each in ARNI and ACEI group. The mean age of the population was 61.2 ± 8.4 years and 62.6 ± 8.6 years in ARNI group and ACEI group, respectively. The mean maximum tolerated dose by population in ARNI group was 203.6 mg and 8.9 mg in ACEI group. Readmission for heart failure were seen significantly higher in ACEI group than ARNI group (p value ¼ 0.001). Parameters like ejection fraction, left ventricular end diastolic and systolic dimensions, 6 min walk test and Kansas City Cardiomyopathy Questionnaires (KCCQ) showed p values < 0.05 between the groups. Conclusion: The ARNI study group showed better safety and efficacy outcomes at the end of 6 months follow-up compared to ACEI group.