Full title: **Effect of sacubitril/valsartan on investigator-reported ventricular arrhythmias in PARADIGM-HF**

Short title: Sacubitril/valsartan and ventricular arrhythmias

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ABSTRACT

Background: Sudden death is a leading cause of mortality in HFrEF. In PARADIGM-HF, sacubitril/valsartan reduced the incidence of sudden death. The purpose of this post hoc study was to analyze the effect of sacubitril/valsartan, compared to enalapril, on the incidence of ventricular arrhythmias.

Methods: Adverse event reports related to ventricular arrhythmias were examined in PARADIGM-HF. The effect of randomized treatment on two arrhythmia outcomes was analyzed: ventricular arrhythmias and the composite of a ventricular arrhythmia, ICD shock or resuscitated cardiac arrest. The risk of death related to a ventricular arrhythmia was examined in time-updated models. The interaction between heart failure aetiology, or baseline ICD/CRT-D use, and the effect of sacubitril/valsartan was analyzed.

Results: Of the 8399 participants, 333 (4.0%) reported a ventricular arrhythmia and 372 (4.4%) the composite arrhythmia outcome. Ventricular arrhythmias were associated with higher mortality. Compared with enalapril, sacubitril/valsartan reduced the risk of a ventricular arrhythmia [HR 0.76 (0.62-0.95); p=0.015] and the composite arrhythmia outcome [HR 0.79 (0.65-0.97); p=0.025]. The treatment effect was maintained after adjustment and accounting for the competing risk of death. Baseline ICD/CRT-D use did not modify effect of sacubitril/valsartan, but aetiology did: HR in patients with an ischaemic aetiology 0.93 (0.71-1.21) versus 0.53 (0.37-0.78) in those without an ischaemic aetiology (p for interaction=0.020).

Conclusions: Sacubitril/valsartan reduced the incidence of investigator-reported ventricular arrhythmias in patients with HFrEF. This effect may have been greater in patients with a non-ischaemic aetiology.

Clinical trial registration: https://www.clinicaltrials.gov unique identifier: NCT01035255 (PARADIGM-HF).

Keywords: neprilysin inhibitor, heart failure, ventricular tachyarrhythmia

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INTRODUCTION

In the Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure trial (PARADIGM-HF)(1), sacubitril/valsartan, compared with enalapril, reduced the risk of death and heart failure hospitalization in patients with heart failure and reduced ejection fraction (HFrEF). Further analysis showed a reduction in both death due to worsening heart failure ("pump failure") and sudden cardiac death(2). Importantly, in PARADIGM-HF, sudden cardiac death was reduced to a similar extent in patients with and without an implanted cardioverter defibrillator (ICD)(3). Although ICDs reduce the risk of sudden death, and rates of sudden death have been declining over time with improving pharmacological therapy(4), this mode of death remains the principal cause of mortality in ambulatory patients with HFrEF.

The reduction in sudden death with sacubitril/valsartan, compared with enalapril, raises the hypothesis that neprilysin inhibition, added to standard care, including a renin angiotensin blocker, reduces the risk of ventricular arrhythmias, although there are other causes of sudden death in patients with heart failure(5). A potential antiarrhythmic action is consistent with the favourable effects of sacubitril/valsartan on left ventricular remodeling, neurohumoral activity, potassium and circulating markers of collagen turnover, potentially reflecting myocardial fibrosis(6-9). In pre-clinical studies, neprilysin inhibition reduces cardiac fibrosis, sympathetic nervous system activity and inducibility of ventricular arrhythmias (10, 11). Several observational clinical case-series have also reported a decrease in frequency of ventricular arrhythmias, after initiation of sacubitril/valsartan(12, 13).

To investigate the hypothesis that sacubitril/valsartan reduces the incidence of ventricular arrhythmias, we undertook a post hoc analysis of PARADIGM-HF, examining adverse event reports of ventricular arrhythmias, ICD discharges or resuscitated cardiac arrest, according to randomized treatment assignment.

METHODS

Study design and participants

PARADIGM-HF was a multicenter, double-blind randomized control trial comparing the effect of treatment with the angiotensin receptor-neprilysin inhibitor (ARNI) sacubitril/valsartan against treatment with an angiotensin-converting enzyme (ACE) inhibitor, enalapril, in patients with HFrEF(1). History of ventricular arrhythmias did not determine eligibility for the trial. Inclusion criteria included a left ventricular ejection fraction (LVEF) of 40% or below and New York Heart Association (NYHA) functional class II, III or IV. Patients were required to have a plasma B-type natriuretic peptide (BNP) level of at least 150 pg per milliliter [or an N-terminal pro-BNP (NT-proBNP) level ≥600 pg per milliliter]. If patients had been hospitalized for heart failure within the previous year, a BNP of at least 100 pg per milliliter (or NT-proBNP ≥400 pg per milliliter) was required. The main exclusion criteria included symptomatic hypotension, a systolic blood pressure (SBP) less than 100 mmHg at screening or 95 mmHg at randomization, an estimated glomerular filtration rate (eGFR) below 30 ml per minute per 1.73 m^2 of body-surface area at screening or at randomization or a decrease in the eGFR of more than 35% between screening and randomization, a serum potassium level of more than 5.2 mmol/L at screening (or above 5.4 mmol/L at randomization), or a history of angioedema or unacceptable intolerance of angiotensin-receptor blocker (ARB) or ACE inhibitor treatment. After screening patients entered a run-in period taking two weeks of enalapril before being switched to sacubitril/valsartan for four to six weeks and then randomized to either treatment in a 1:1 ratio. The trial was conducted in accordance with the Declaration of Helsinki, was approved by an ethics committee at each study center and all patients provided written informed consent. The design and main findings of PARADIGM-HF are published(1, 14).

Prespecified trial outcomes

The primary composite outcome in PARADIGM-HF was time to cardiovascular death or first heart failure hospitalization, whichever occurred first. All-cause death was a secondary outcome. All occurrences of death and suspected heart failure hospitalization were adjudicated against standardized criteria by a blinded clinical endpoints committee (CEC) at the Brigham and Women's Hospital, Boston, MA. Where possible, death was classified as cardiovascular or non-cardiovascular and cardiovascular deaths were further subclassified into categories which included sudden death and pump failure death (sudden death was defined only as death occurring unexpectedly in an otherwise stable patient). Patients who were resuscitated from cardiac arrest were also identified (meaningful recovery of consciousness following successful cardioversion, defibrillation or cardiopulmonary resuscitation). Patients resuscitated from a cardiac arrest, confirmed by adjudication, were included in the analysis of the composite of time-to-first occurrence of a ventricular arrhythmia or ICD discharge or resuscitated cardiac arrest.

Identification of ventricular arrhythmias

All adverse events reported by investigators during PARADIGM-HF were examined for any report of a ventricular arrhythmia or an ICD discharge. The adverse events were identified using the MedDRA preferred terms “ventricular tachycardia (sustained and non-sustained)” (VT), “ventricular fibrillation” (VF), “ventricular flutter”, “torsades de pointes”, “ventricular tachyarrhythmia” and “ventricular arrhythmia”. Adverse events were not reviewed by a blinded committee unless one of the pre-specified endpoints occurred (eg a sudden death or resuscitated cardiac arrest) in which case the events were classed according to the committee’s adjudication. A serious adverse event (SAE) was defined as an event which was either fatal or life-threatening, resulted in persistent significant disability or

incapacity, caused or prolonged a hospitalization, constituted a congenital anomaly/birth defect or was medically significant (requiring a medical or surgical intervention to prevent one of the other outcomes listed).

Two time-to-first event ventricular arrhythmia outcomes were examined: 1) any ventricular arrhythmia and 2) the composite of a ventricular arrhythmia, resuscitated cardiac arrest or an ICD discharge. For the purposes of this analysis, ventricular arrhythmias were defined as VT, VF, ventricular flutter, torsades de pointes, ventricular tachyarrhythmia and ventricular arrhythmia (reflecting MedDRA preferred terms used for reporting adverse events). Premature ventricular ectopic events were not included in this analysis. For participants who experienced more than one type of ventricular arrhythmia, only the first event was included in the analysis of the composite endpoint.

Statistical Analysis

Baseline characteristics were compared for participants experiencing no ventricular arrhythmia, any ventricular arrhythmia, or a ventricular arrhythmia/ICD discharge/resuscitated cardiac arrest. Categorical variables are reported as whole numbers with percentages. Continuous variables are reported by their mean value with standard deviations or median value plus interquartile ranges depending on a respective normal or skewed distribution. The effect of sacubitril/valsartan compared with enalapril on the incidence of each ventricular arrhythmia outcome was examined in a time-to-first event analysis using Cox proportional hazards regression models. Additionally, we examined the effect of sacubitril/valsartan, compared with enalapril, on the narrower composite of VT, VF, ventricular flutter or torsades de pointes (i.e., excluding the MedDRA preferred terms "ventricular tachyarrhythmia" and "ventricular arrhythmia"). In a further sensitivity analysis, we examined each of the ventricular arrhythmia outcomes including only events that were

reported as SAEs. The primary models included factors for randomized treatment assignment and the randomization stratification variable of region. Multivariable models were adjusted for factors known to influence prognosis including beta-blocker use, ACE inhibitor or ARB use, mineralocorticoid receptor antagonist (MRA) use, ischaemic aetiology, LVEF, presence of an ICD or cardiac resynchronization therapy (CRT) device, eGFR, NYHA class, hypertension, diabetes, past hospitalization for heart failure, log transformed NT-proBNP. Event rates per 100 patient years were calculated and are presented with 95% confidence intervals (CIs). The cumulative incidences of outcomes are presented graphically using the Kaplan-Meier method. To account for the fact that death precludes the future occurrence of ventricular arrhythmias, a proportional hazards competing risk regression model was used as a sensitivity analysis (15). To examine the relative hazard of mortality before or after the occurrence of a ventricular arrhythmia, Cox proportional-hazard regression models were performed with the occurrence of ventricular arrhythmia or the composite outcome modelled as a time-varying covariate(16). The effect of randomized treatment was examined in Cox proportional-hazard regression models, and the interaction with randomized therapy tested in two important subgroups. The first group was patients with an ischaemic or non-ischaemic aetiology for heart failure and the second patients with or without an implanted defibrillating device at baseline. The relationship between change in NT-proBNP from baseline to 8 months and the incidence of ventricular arrhythmias was examined using change in NT-proBNP modelled as a continuous variable in a restricted cubic spline model adjusted for baseline value. Only arrhythmic events occurring after 8 months were included.

A p-value <0.05 was considered statistically significant. Statistical analyses were performed using Stata 16.1 (College Station, Texas, USA).

RESULTS

A total of 8399 patients were included in the present analysis, of whom 333 patients (4.0%) had a report of a ventricular arrhythmia. The events accounting for a ventricular arrhythmia included VT in 246 patients (241 as a first event), VF in 64 patients (60 as a first event), ventricular flutter in 1 patient (1 as a first event), torsades de pointes in 2 patients (2 as a first event), a "ventricular tachyarrhythmia" in 1 patient (0 as a first event) and a "ventricular arrhythmia" in 33 patients (29 as a first event). Among the 246 patients experiencing VT, 43 patients had non-sustained VT (35 as a first event). **Figure 1** outlines the occurrence of adjudicated fatal events and resuscitated cardiac arrest in patients who had a ventricular arrhythmia reported. 200 of 333 (60.1%) first ventricular arrhythmia events were reported as SAEs.

A total of 372 patients (4.4%) experienced the composite of a ventricular arrhythmia, an ICD shock or resuscitated cardiac arrest. Among these 372 patients, the first event was a ventricular arrhythmia in 311 patients. An ICD shock was reported in 31 participants (23 as a first event) and resuscitated cardiac arrest in 44 patients (38 as a first event). The occurrence of adjudicated fatal events in patients who experienced this composite outcome is outlined in **Figure S1 (Online Supplement)**.

Baseline characteristics

The baseline characteristics of patients who did and did not experience a ventricular arrhythmia are shown in ***Table 1***. Compared to those without a report of a ventricular arrhythmia, patients with a report of a ventricular arrhythmia were more likely to be male, White, to have a longer duration of heart failure, and a history of myocardial infarction. Heart rate, SBP, eGFR and LVEF were lower in patients with a report of a ventricular arrhythmia, but BMI was higher. Age, NYHA class, and KCCQ Clinical Summary Score did not differ

between these two groups. Patients with a report of a ventricular arrhythmia after randomization were more likely to have a history of previous ventricular arrhythmia, to be treated with amiodarone and to have an ICD or received cardiac resynchronization therapy with a defibrillator. Participants with a report of a ventricular arrhythmia also had a wider QRS duration (but no excess of either right or left bundle branch block) and were less likely to have atrial fibrillation on their baseline ECG, although the proportion of patients with a history of atrial fibrillation did not differ between the groups.

NT-proBNP level did not differ between patients with and without a ventricular arrhythmia, but troponin and urinary cGMP levels were higher in patients with a ventricular arrhythmia. Sodium, potassium, and other biomarkers, including aldosterone and galectin-3 did not differ between patients with and without a ventricular arrhythmia. The pattern of differences described was essentially identical when comparing patients with a report of a ventricular arrhythmia, ICD discharge or resuscitated cardiac arrest, to those with no report of a ventricular arrhythmia.

Effect of randomized treatment on incidence of ventricular arrhythmias

Table 2 shows the incidence of the ventricular arrhythmia outcomes, according to randomized treatment. Compared to patients randomly assigned to enalapril, participants assigned to sacubitril/valsartan had lower rate of ventricular arrhythmia (HR 0.76 [95%CI 0.62-0.95], p=0.015) and the composite outcome of a ventricular arrhythmia, ICD shock or resuscitated cardiac arrest (HR 0.79 [95%CI 0.65-0.97], p=0.025) ***[Graphical abstract, Figure 2 and 3]***. The rate of the narrower ventricular arrhythmia composite of VT, VF, ventricular flutter or torsades de pointes events was also lower in patients treated with sacubitril/valsartan compared to enalapril (HR 0.77 [95%CI 0.62 – 0.97], p=0.027). The effect of treatment was essentially unchanged in the multivariable adjusted analyses. In a

sensitivity analysis including only ventricular arrhythmia events that were reported as SAEs the favourable effect of a reduction in ventricular arrhythmias when treated with sacubitril/valsartan, compared to enalapril, was consistent with the main analysis findings (***Online Supplement Table S1***). Analyses modelling all-cause mortality as a competing risk, also gave similar results (***Online Supplement Table S2 and Online Supplement Figure S1a and S1b***) for the ventricular arrhythmia outcome and the composite ventricular arrhythmia, ICD shock or resuscitated cardiac arrest.

Effect of sacubitril/valsartan on ventricular arrhythmias according to heart failure aetiology and baseline implanted defibrillator use

Of the 5036 patients with an ischaemic aetiology, 216 (4.3%) experienced at least one ventricular arrhythmia; the corresponding number for the 3363 patients without an ischaemic aetiology was 117 (3.5%). The hazard ratio for the effect of sacubitril/valsartan, compared with enalapril, on ventricular arrhythmias in patients with an ischaemic aetiology was 0.93 (95%CI 0.71-1.21), compared with 0.53 (95%CI 0.37-0.78) in those without an ischaemic aetiology (p for interaction=0.020) ***[Table 3]***.

Of the 1243 patients with a defibrillating device (ICD or CRT-D) implanted at baseline, 165 (13.3%) experienced at least one ventricular arrhythmia. Among the 7,156 participants without a defibrillating device, 168 (2.3%) experienced at least one ventricular arrhythmia. The hazard ratio for the effect of sacubitril/valsartan, compared with enalapril, on ventricular arrhythmias in patients with an ICD/CRT-D was 0.77 (95%CI 0.57-1.05) compared with 0.76 (95%CI 0.56-1.04) in those without such a device (p for interaction=0.952) ***[Table 3]***.

Association between any report of a ventricular arrhythmia and subsequent mortality

When occurrence of ventricular arrhythmia was modelled as a time-varying covariate there was a strong association with mortality. For a ventricular arrhythmia, the unadjusted HR for all-cause mortality was 3.89 (95%CI 3.19-4.75), p<0.001; and for the composite of a ventricular arrhythmia, ICD shock or resuscitated cardiac arrest, the HR for all-cause mortality was 3.86 (95%CI 3.19-4.67), p<0.001. The corresponding adjusted HRs were 4.15 (95%CI 3.39-5.09); p<0.001; and 4.06 (95%CI 3.34-4.93); p<0.001, respectively. The occurrence of a ventricular arrhythmia was also associated with cardiovascular death and both heart failure (adjusted HR 4.93 (3.38-7.19); p<0.001) and sudden death (adjusted HR 3.38 (2.22-5.15); p<0.001) (***Online Supplement Table S3a and S3b***).

Association between any report of a ventricular arrhythmia and change in NT-proBNP

Data were available to calculate change in NT-proBNP between baseline and 8 months in 1798 patients. When change in NT-proBNP was modelled as a continuous variable, an increase in NT-proBNP >3255pg/ml was associated with a higher incidence of ventricular arrhythmia (***Online Supplement Figure S2).***

DISCUSSION

The main findings of this analysis were that sacubitril/valsartan reduced the risk of investigator-reported ventricular arrhythmias in patients with HFrEF, the occurrence of which was strongly associated with subsequent death.

Ambulatory monitoring and other systematic approaches to arrhythmia detection identify ventricular premature beats and non-sustained ventricular tachycardia in most patients with HFrEF(17-19). The rate of ventricular arrhythmias detected in the present study was lower because they were identified through spontaneous adverse event reporting by investigators, rather than by systematic monitoring. However, in our recent report from the DAPA-HF trial using a similar approach to identify arrhythmic events, the rate of ventricular arrhythmias was almost identical to that observed in PARADIGM-HF(20). Events reported spontaneously probably reflect the most clinically significant episodes, compared with the more complete burden identified by systematic monitoring(21). The view that spontaneously reported events are the more clinically significant episodes is also supported by the high subsequent mortality rate in patients with an adverse event report of this type in PARADIGM-HF. When analyzed as a time-varying covariate, the occurrence of a ventricular arrhythmia was associated with a 3 to 4-fold increased risk of death. In past studies, there has been an inconsistent association between non-sustained ventricular tachycardia and mortality in patients with HFrEF, especially when other prognostic variables were accounted for(17, 21, 22). However, despite extensive adjustment, including for NT-proBNP, an adverse event report of a ventricular arrhythmia remained an independent and statistically significant predictor of death in PARADIGM-HF. The effectiveness of sacubitril/valsartan in reducing sudden death has been clearly demonstrated in the PARADIGM-HF trial(2). The present

analysis adds mechanistic insight into this benefit, through a reduction in potentially lethal ventricular arrhythmias.

The baseline characteristics of participants with adverse event reports related to a ventricular arrhythmia were also consistent with what would be expected in patients at high risk of such events, including male sex, history of coronary disease, lower LVEF, more frequent treatment with amiodarone and higher rates of prior ventricular arrhythmia and device implantation(23, 24). We also examined a composite of clinically more severe events, in which we included ICD shocks and patients experiencing cardiac arrest who were resuscitated, in addition to adverse event reports of ventricular tachycardia and fibrillation, whichever occurred first. Neither of the former were common, adding only 23 ICD discharge and 28 resuscitated cardiac arrest first events.

Whether we analyzed an adverse event report of a ventricular arrhythmia or the composite of ventricular tachycardia, ventricular fibrillation, ICD shock or resuscitated cardiac arrest, sacubitril/valsartan reduced these events by approximately 20%, compared with enalapril. Although enalapril was shown not to reduce the frequency or complexity of ventricular arrhythmias in patients with HFrEF in the Studies Of Left Ventricular Dysfunction(25), both beta-blockers and MRAs reduce ventricular arrhythmias and sudden death and the rate of use of these other therapies was high in PARADIGM-HF(26-29). The effect of sacubitril/valsartan on ventricular arrhythmias has not been studied in any prior randomized trial, although our findings are consistent with the reduction in sudden cardiac death reported in PARADIGM-HF and several observational analyses of the effect of sacubitril/valsartan on the burden of ventricular arrhythmias in patients with HFrEF(12, 13, 30). For example, in a single center study of 167 HFrEF patients with dual chamber ICD,

Russo and colleagues observed significantly fewer episodes of ventricular fibrillation and ventricular tachycardia, both sustained and non-sustained, and appropriate ICD shock events, over a period of up to 12 months after starting sacubitril/valsartan, compared to before treatment(12). Similar findings have been reported in other smaller studies(13, 30).

Ventricular arrhythmias were reported more commonly in patients with an implanted defibrillating device. We were unable to tell whether the higher incidence of ventricular arrhythmias in patients with devices reflected the reason why they had the device (i.e., because of a prior arrhythmia or for primary prevention in a patient at perceived high-risk) or because of the ability of the device to detect arrhythmias. Our findings support the recent recommendation in the ESC guidelines on the management of heart failure that the implantation of a primary prevention guideline is delayed until medical therapy has been optimized for at least three months in the hope that the LVEF may increase to above 35%, obviating the need for an ICD(31). Although this strategy may cause concern about the risk of early sudden death, the absolute rate in a 90-day period is very small, especially in lower-risk patients such as those with non-ischaemic cardiomyopathy(32). Moreover, most recommended pharmacological therapies, as well as (or maybe because of) improving LVEF, also reduce the risk of sudden death. The data reported in this paper and our recent findings with dapagliflozin(20) extend this evidence to these newer recommended therapies and show that their benefit is additional to that of RAS blockers, beta-blockers and MRAs. However, we found that sacubitril/valsartan reduced arrhythmias to a similar extent in patients with and without such devices. The decision of whether to implant an ICD and the appropriate timing to do so, particularly in patients with a non-ischaemic aetiology for heart failure, remains a subject of debate since the results of the DANISH trial were reported(32). The recent 2021 ESC heart failure guidelines reduced the strength of recommendation for ICD implantation in

patients with a non-ischaemic aetiology from Class I to Class IIa, with the recommendation that medical therapy should be optimized over a minimum of 3 months before implantation of a device(31). Our data support this recommendation, especially as sacubitril/valsartan has favourable effects on cardiac remodelling and may obviate the need for an ICD should the LVEF increase to more than 35%(8). Conversely, sacubitril/valsartan seemed to be more effective in reducing ventricular arrhythmias in patients with a non-ischaemic aetiology, compared to an ischaemic aetiology. Patients with an ischaemic aetiology in PARADIGM-HF were more likely to have an ICD than non-ischaemic patients (16.5% versus 12.2%, $p<0.001$) which may have attenuated the potential benefit of sacubitril/valsartan in these patients. Extensive scar after myocardial infarction may also represent an arrhythmia substrate that responds less favourably to sacubitril/valsartan. In this context, the TAROT-HF study showed more favourable cardiac remodelling with sacubitril/valsartan in non-ischaemic patients compared to those with an ischaemic aetiology(33).

The mechanisms by which sacubitril/valsartan affects ventricular arrhythmias are unknown(34). Sacubitril/valsartan did not affect cardiac repolarization in healthy human volunteers(35) although, recently, neprilysin inhibition with sacubitrilat (the active metabolite of sacubitril) was shown to directly decrease potentially pro-arrhythmogenic diastolic sarcoplasmic reticulum calcium leak in human ventricular cardiomyocytes from patients with end-stage heart failure(36). Other potential mechanisms have been suggested by studies in experimental animals, where the combination of a neprilysin inhibitor with a renin-angiotensin system blocker reduces cardiac fibrosis and remodeling, compared to renin-angiotensin system blockade alone(36-39). Chamber dilatation and myocardial stretch, reflected in elevation of natriuretic peptide levels, are associated with the occurrence of ventricular arrhythmias. In two randomized trials and one observational study in patients with HFrEF, sacubitril/valsartan reduced cardiac chamber size, and sacubitril/valsartan also

reduced NT-proBNP level, consistent with decreased wall stress(7, 8, 40). These actions would be expected to reduce the propensity to ventricular arrhythmias. Indeed, we found a relationship between increasing NT-proBNP over time and risk of ventricular arrhythmia, consistent with this hypothesis. This is consistent with the findings of Rohde et al that the reduction in risk of sudden death with sacubitril/valsartan, compared with enalapril, tended to be greater in patients with a non-ischaemic aetiology(3). It is also possible that more favourable cardiac remodeling with sacubitril/valsartan in non-ischaemic patients, as suggested by the TAROT-HF study, might explain the greater reduction in ventricular arrhythmias in these participants, compared to patients with an ischaemic aetiology(33). Lastly, the accuracy of the aetiological classification of heart failure depends on the extent of investigation and this varies globally. Therefore, some patients thought to have a non-ischaemic aetiology may have had undiagnosed coronary disease.

Finally, while there is a clear link between ventricular arrhythmias and sudden death, it is important to note that not all sudden deaths are due to an arrhythmia or indeed any electrical disturbance, which is why ICDs do not eliminate the risk of sudden death. In this context, it is important to note that sacubitril/valsartan also appeared to reduce the risk of sudden death in patients with an ICD, although this analysis was based on a small number of events(2). Conversely, ventricular arrhythmias are also predictive of non-sudden death because they are often a marker of a sicker patient with worse ventricular function or more advanced heart failure as found in the present analyses.

Our study has several limitations. Firstly, this was not a prespecified analysis. Secondly, our analysis relied on adverse event reporting which will have resulted in underestimation of the overall prevalence of ventricular arrhythmias. We were unable to

ascertain whether ICD discharges were appropriate or inappropriate and did not have information on anti-tachycardia pacing. There was no electrocardiographic validation of arrhythmias and standardized criteria for reporting of specific ventricular arrhythmias were not provided. However, a similar approach to the one used in the present study identified a benefit of a beta-blocker on arrhythmias in patients with left ventricular systolic dysfunction, consistent with that found in studies using systematic monitoring(21). Nevertheless, our findings could be strengthened in future trials by systematic assessment of ventricular arrhythmias using either ambulatory monitoring or by using implanted cardiac devices.

In summary, in this post hoc analysis, sacubitril/valsartan, compared with enalapril, reduced the incidence of investigator-reported (but not adjudicated) ventricular arrhythmias in patients with HFrEF, most of whom were treated with a beta-blocker and, in over half of cases, an MRA as well. This possible antiarrhythmic effect is additional to the known benefits of sacubitril/valsartan in HFrEF.

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CONFLICTS OF INTEREST

Dr Desai reported receiving personal fees from Abbott, Biofourmis, Boston Scientific, Boehringer Ingelheim, Merck, Regeneron, and Relypsa and grants and personal fees from AstraZeneca, Alnylam, and Novartis outside the submitted work. Dr Lefkowitz is an employee of Novartis. Dr Packer has received consulting fees from AbbVie, Akcea, Actavis, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cardiorentis, Daiichi Sankyo, Gilead, Johnson & Johnson, Novo Nordisk, Pfizer, Relypsa, Sanofi, Synthetic Biologics, and Theravance. Dr Rouleau has received grants and consulting fees from Novartis and consulting fees from Abbott, AstraZeneca, MyoKardia, and Sanofi. Dr Rohde has been a consultant or served on advisory board for Amgen, Astra- Zeneca, Merck and Novartis. Dr Swedberg reports consulting for Novartis. Dr Zile has received research funding from Novartis and has been a consultant for Novartis, Abbott, Boston Scientific, CVRx, EBR, Endotronics, Ironwood, Merck, Medtronic, and Myokardia V Wave. Dr Petrie has received lecture fees from AstraZeneca and Eli Lilly, personal fees from Novo Nordisk, AstraZeneca, NAPP Pharmaceuticals, Takeda Pharmaceutical, Alnylam, Bayer, Resverlogix, and Cardiorentis and grants and personal fees from Boehringer Ingelheim and Novartis. Dr Jhund has received consulting fees, advisory board fees, and lecture fees from Novartis; advisory board fees from Cytokinetics; and grant support from Boehringer Ingelheim. Dr Solomon has received research grants from Actelion, Alnylam, Amgen, AstraZeneca, Bellerophon, Bayer, BMS, Celladon, Cytokinetics, Eidos, Gilead, GSK, Ionis, Lilly, Lone Star Heart, Mesoblast, MyoKardia, NIH/NHLBI, Neurotronik, Novartis, NovoNordisk, Respicardia, Sanofi Pasteur, Theracos, and has consulted for Abbott, Action Akros, Alnylam, Amgen, Arena, AstraZeneca, Bayer, Boeringer-Ingelheim, BMS, Cardior, Cardurion, Corvia, Cytokinetics, Daiichi-Sankyo, Gilead, GSK, Ironwood, Lilly, Merck, Myokardia, Novartis, Roche, Takeda, Theracos, Quantum Genetics, Cardurion, AoBiome, Janssen, Cardiac Dimensions, Tenaya,

Sanofi-Pasteur, Dinaqor, Tremeau, CellProThera, Moderna, American Regent. Dr McMurray has received payments through Glasgow University from work on clinical trials, consulting and other activities from Alnylam, Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Cardurion, Cytokinetics, DalCor, GSK, KBP Biosciences, Novartis, Pfizer, Theracos; and personal payments from Abbott, Hikma, Ionis, Sun Pharmaceuticals, Servier. The other authors report no conflicts.

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LEGENDS

Graphical Abstract.

Figure 1. Incidence of adjudicated fatal events and resuscitated cardiac arrest in patients with a reported ventricular arrhythmia

Figure 2. Kaplan Meier curves for time to first ventricular arrhythmia / ICD shock / resuscitated cardiac arrest according to treatment assignment

Figure 3. Kaplan Meier curves for time to first ventricular arrhythmia / ICD shock / resuscitated cardiac arrest according to treatment assignment

Online Supplement Figure S1. Incidence of adjudicated fatal and non-fatal events in patients who experienced a ventricular arrhythmia / ICD shock / resuscitated cardiac arrest

Online Supplement Figure S2a. Cumulative incidence of first ventricular arrhythmia in a competing risks regression according to treatment assignment

Online Supplement Figure S2b. Cumulative incidence of first ventricular arrhythmia / ICD shock / resuscitated cardiac arrest in a competing risks regression according to treatment assignment

Online Supplement Figure S3. Restricted cubic spline of the relationship between change in NT-ProBNP (range -10000 pg/ml to +10000 pg/ml) from baseline to 8 months and the incidence of ventricular arrhythmia.

Table 1. Baseline characteristics of participants who had no ventricular arrhythmia compared with those who had a ventricular arrhythmia and the composite of a ventricular arrhythmia / ICD shock / resuscitated cardiac arrest

	No ventricular arrhythmia	Ventricular arrhythmia*	P Value†	Ventricular arrhythmia / ICD shock / resuscitated cardiac arrest‡	P Value†
n = (%)	8066 (96.0)	333 (4.0)		372 (4.4)	
Age (years)	64 ± 11	64 ± 11	0.450	64 ± 11	0.570
Race (%)			<0.001		<0.001
White	5291 (65.6)	253 (76.0)		277 (74.5)	
Black	406 (5.0)	22 (6.6)		27 (7.3)	
Asian	1477 (18.3)	32 (9.6)		37 (9.9)	
Other	892 (11.1)	26 (7.8)		31 (8.3)	
Region (%)			<0.001		<0.001
North America	538 (6.7)	64 (19.2)		73 (19.6)	
Latin America	1388 (17.2)	45 (13.5)		52 (14.0)	

Western Europe	1920 (23.8)	131 (39.3)		143 (38.4)	
Central Europe	2764 (34.3)	62 (18.6)		68 (18.3)	
Asia-Pacific & Other	1456 (18.1)	31 (9.3)		36 (9.7)	
Sex (%)					
Male	6282 (77.9)	285 (85.6)	<0.001	320 (86.0)	<0.001
SBP (mmHg)	122 ± 15	118 ± 15	<0.001	117 ± 15	<0.001
Heart rate (bpm)- Sinus	72 ± 11	69 ± 11	0.002	69 ± 11	<0.001
Heart rate (bpm)- AF /flutter§	74 ± 13	69 ± 12	<0.001	70 ± 12	0.002
BMI (kg/m^2)	28 ± 6	29 ± 6	0.003	29 ± 6	0.003
eGFR (ml/min/1.73m^2)	68 ± 20	64 ± 22	<0.001	64 ± 21	<0.001
eGFR <60 ml/min/1.73m^2	2908 (36.1)	153 (45.9)	<0.001	173 (46.5)	<0.001
LVEF (%) (IQR) ‖	30 (25 – 34)	30 (25 – 33)	<0.001	30 (25 – 32)	<0.001
LVEF			0.002		<0.001
< median	3218 (39.9)	161 (48.3)		184 (49.5)	
≥ median	4847 (60.1)	172 (51.7)		188 (50.5)	

NT-ProBNP (pg/ml) (IQR)- No AF/flutter§	1447 (814 - 2955)	1377 (768 – 3111)	0.880	1477 (775 – 3140)	0.920
NT-ProBNP (pg/ml) (IQR)- AF/flutter§	1885 (1095 – 3646)	1981 (1053 – 3954)	0.850	2009 (1138 – 3976)	0.590
Troponin (µg/L) #	0.015 (0.010 – 0.023)	0.018 (0.012 – 0.026)	0.013	0.017 (0.011 – 0.025)	0.055
Plasma Aldosterone (pmol/L) #	243 (152 – 386)	258 (159 – 372)	0.420	268 (160 – 386)	0.230
Galectin (ng/ml) #	18.7 ± 6.9	18.6 ± 6.7	0.800	18.8 ± 6.8	0.940
Cystatin C (mg/L) #	1.2 ± 0.4	1.2 ± 0.4	0.400	1.2 ± 0.4	0.270
Urinary cyclic-GMP (nmol/L) #	1109 (683 – 1813)	1417 (827 – 1956)	0.015	1397 (827 – 1920)	0.021
Potassium (mmol/L)	4.5 ± 0.5	4.5 ± 0.5	0.680	4.5 ± 0.5	0.760
Sodium (mmol/L)	141 ± 3	141 ± 3	0.300	141 ± 3	0.097
RBBB	604 (7.5)	23 (6.9)	0.690	24 (6.5)	0.450
LBBB	1583 (19.6)	70 (21.0)	0.530	79 (21.2)	0.440
QRS duration (ms)	117 ± 36	134 ± 35	<0.001	134 ± 35	<0.001
NYHA Class (%)			0.120		0.200

I	379 (4.7)	10 (3.0)		12 (3.2)	
II	5666 (70.4)	253 (76.0)		280 (75.3)	
III	1949 (24.2)	69 (20.7)		78 (21.0)	
IV	59 (0.7)	1 (0.3)		2 (0.5)	
KCCQ-CSS median (IQR) ‖	80 (63 - 92)	80 ± (67 – 91)	0.840	80 (67 – 91)	0.800
Medical History (%)					
Duration of heart failure			<0.001		<0.001
<1 year	2455 (30.7)	45 (13.5)		52 (14.0)	
1 – 5 years	3085 (38.6)	118 (35.4)		131 (35.2)	
>5 years	2445 (30.6)	170 (51.1)		189 (50.8)	
Ischaemic aetiology	4820 (59.8)	216 (64.9)	0.062	239 (64.2)	0.084
Previous ventricular arrhythmia	185 (2.3)	47 (14.1)	<0.001	50 (13.4)	<0.001
Hypertension	5716 (70.9)	224 (67.3)	0.160	256 (68.8)	0.410

Diabetes	2768 (34.3)	128 (38.4)	0.120	139 (37.4)	0.230
AF history	2951 (36.6)	107 (32.1)	0.098	127 (34.1)	0.350
AF/flutter on baseline ECG	2036 (25.2)	54 (16.2)	<0.001	64 (17.2)	<0.001
Prior HF hospitalization	5069 (62.8)	205 (61.6)	0.640	232 (62.4)	0.860
MI	3460 (42.9)	174 (52.3)	<0.001	196 (52.7)	<0.001
PCI	1702 (21.1)	99 (29.7)	<0.001	112 (30.1)	<0.001
CABG	1215 (15.1)	88 (26.4)	<0.001	97 (26.1)	<0.001
Stroke	693 (8.6)	32 (9.6)	0.520	35 (9.4)	0.590
COPD	1035 (12.8)	45 (13.5)	0.720	52 (14.0)	0.510
Anaemia**	1626 (20.2)	66 (19.8)	0.880	76 (20.4)	0.890
Medical Therapy (%)					
Loop diuretic	6053 (75.0)	264 (79.3)	0.079	294 (79.0)	0.081
Thiazide / Thiazide-related diuretic	1133 (14.0)	52 (15.6)	0.420	57 (15.3)	0.490
Prior ACE inhibitor	6275 (77.8)	257 (77.2)	0.790	287 (77.2)	0.770
Prior ARB	1814 (22.5)	78 (23.4)	0.690	89 (23.9)	0.510

Beta-blocker	7500 (93.0)	311 (93.4)	0.770	350 (94.1)	0.400
MRA	4847 (60.1)	184 (54.8)	0.078	208 (55.9)	0.110
Digoxin	2449 (30.4)	90 (27.0)	0.190	107 (28.8)	0.530
Amiodarone	728 (9.0)	55 (16.5)	<0.001	62 (16.7)	<0.001
Sotalol	37 (0.5)	4 (1.2)	0.057	4 (1.1)	0.097
ICD or CRT-D	1078 (13.4)	165 (49.5)	<0.001	182 (48.9)	<0.001
CRT-D	371 (4.6)	53 (15.9)	<0.001	59 (15.9)	<0.001
CRT-P	145 (1.8)	5 (1.5)	0.690	6 (1.6)	0.800

*Ventricular arrhythmia was defined as any adverse event report using the MedDRA preferred terms “ventricular tachycardia” (VT), “ventricular fibrillation”, “ventricular flutter”, “torsades de pointes”, “ventricular tachyarrhythmia” and “ventricular arrhythmia”. Premature ventricular ectopics were excluded.

†P value compared to no ventricular arrhythmia

‡372 patients with a ventricular arrhythmia / ICD shock / resuscitated cardiac arrest compared to 8027 patients with no ventricular arrhythmia

§ Based on a history of atrial fibrillation (AF) or baseline ECG documenting AF or atrial flutter

|| Plus-minus values are means ± standard deviations. IQR denotes interquartile range

#Biomarkers measured in subset of patients: plasma troponin n= 1947; plasma aldosterone n= 1976; galectin-3 n= 2043; cystatin C n= 2056; urinary cyclic-GMP n= 2033

**Anaemia was defined as Hb <130 g/L in males and Hb <120 g/L in females

ACE = angiotensin converting enzyme; AF = atrial fibrillation; ARB = angiotensin receptor blocker; BMI = body mass index; CABG = coronary bypass graft; COPD = chronic obstructive pulmonary disease; CRT-D = cardiac resynchronization therapy- defibrillator; CRT-P = cardiac resynchronization therapy- pacemaker; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; HF = heart failure; ICD = implantable cardioverter defibrillator; KCCQ CSS = Kansas City Cardiomyopathy Questionnaire clinical summary score; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; MI = myocardial infarction; MRA = mineralocorticoid receptor antagonist; NT-ProBNP = N-terminal pro B-type natriuretic peptide; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; RBBB = right bundle branch block; SBP = systolic blood pressure

Table 2. Cox proportional-hazard models for each ventricular arrhythmia outcome according to randomized treatment assignment

	Sacubitril / Valsartan		Enalapril		Primary Analysis*	Adjusted Analysis†
Outcome	**n/N (%)**	**Event Rate per 100 patient years (95%CI)**	**n/N (%)**	**Event Rate per 100 patient years (95%CI)**	**Hazard Ratio (95%CI)**	**Hazard Ratio (95%CI)**
Ventricular arrhythmia	145/4187 (3.5)	1.6 (1.4-1.9)	188/4212 (4.5)	2.1 (1.8-2.4)	0.76 (0.62-0.95); p=0.015	0.78 (0.62-0.96); p=0.021
Ventricular arrhythmia / ICD shock / Resuscitated cardiac arrest	165/4187 (3.9)	1.8 (1.6-2.1)	207/4212 (4.9)	2.3 (2.0-2.6)	0.79 (0.65-0.97); p=0.025	0.81 (0.66-0.99); p=0.039

VT / VF / Ventricular flutter / Torsades de pointes	133/4175 (3.2)	1.5 (1.2-1.7)	171/4195 (4.1)	1.9 (1.6-2.2)	0.77 (0.62-0.97); p=0.027	0.79 (0.63-0.99); p=0.043

***Primary analysis** included randomized treatment and region

†**Adjusted analysis** included randomized treatment, region, beta-blocker use, ACE inhibitor use, ARB use, mineralocorticoid receptor antagonist use, ischaemic aetiology, ejection fraction, presence of implanted cardioverter defibrillator or cardiac resynchronization therapy, NYHA class, hypertension, diabetes, past hospitalization for heart failure, eGFR, log transformed NT-ProBNP

Table 3. Cox proportional-hazard models for a ventricular arrhythmia outcome according to randomized treatment assignment in two key patient subgroups

	Sacubitril / Valsartan		Enalapril		Unadjusted Analysis*	Adjusted Analysis†	Interaction P-Value
Outcome	**n/N (%)**	**Event Rate per 100 patient years (95%CI)**	**n/N (%)**	**Event Rate per 100 patient years (95%CI)**	**Hazard Ratio (95%CI)**	**Hazard Ratio (95%CI)**	
Ischaemic aetiology							
Yes	103/2506 (4.1)	1.9 (1.6-2.3)	113/2530 (4.5)	2.1 (1.7-2.5)	0.93 (0.71-1.21)	0.92 (0.70-1.20)	0.020
No	42/1681 (2.5)	1.1 (0.8-1.5)	75/1682 (4.5)	2.1 (1.7-2.6)	0.53 (0.37-0.78)	0.57 (0.39-0.83)	
ICD/CRT-D at baseline							
Yes	72/623 (11.6)	5.4 (4.3-6.8)	93/620 (15.0)	7.0 (5.7-8.6)	0.77 (0.57-1.05)	0.81 (0.59-1.11)	0.952

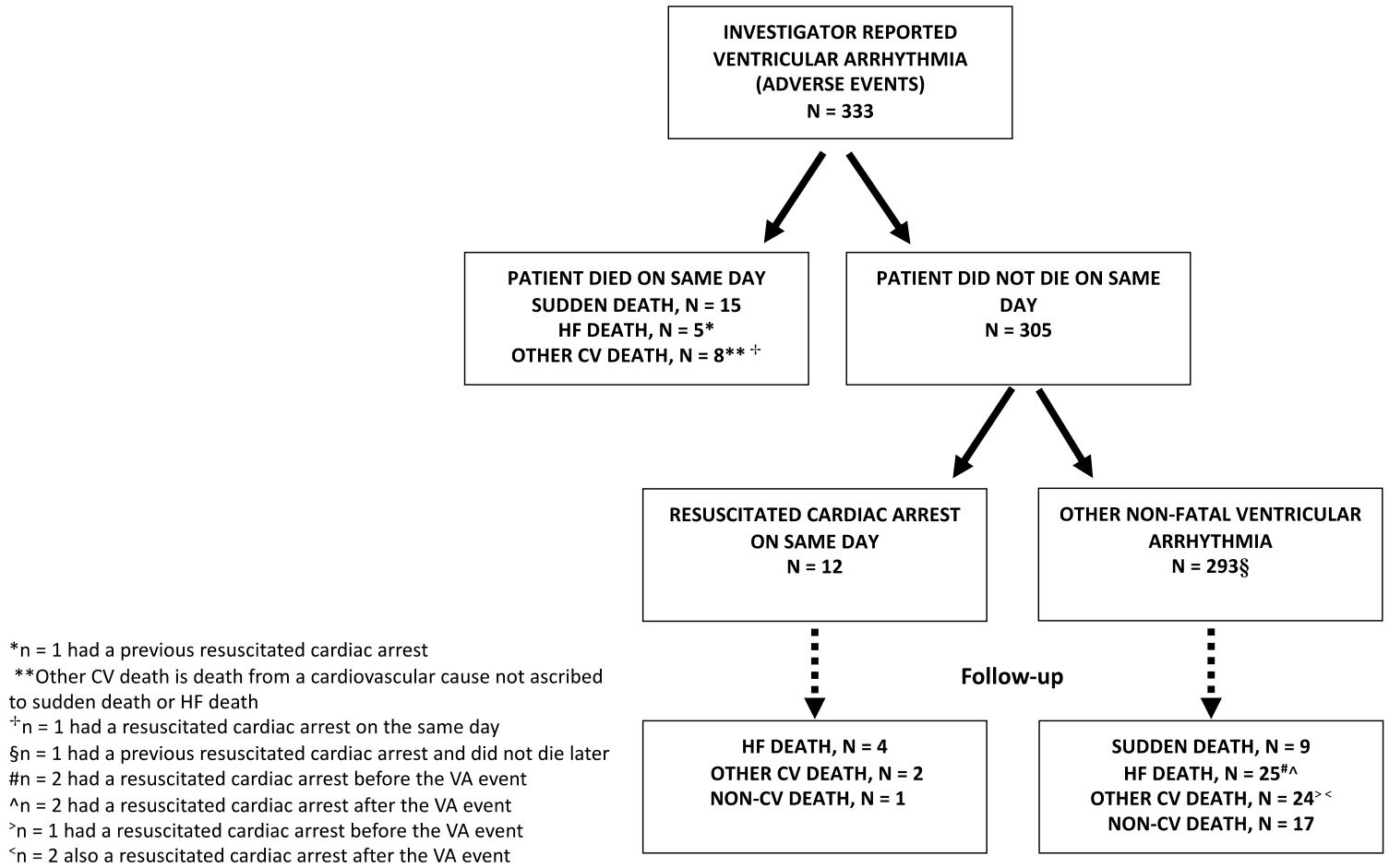
No	73/3564 (2.0)	0.9 (0.7-1.2)	95/3592 (2.6)	1.2 (1.0-1.5)	0.76 (0.56-1.04)	0.76 (0.56-1.04)	

***Unadjusted analysis** included randomized treatment and region

†**Adjusted analysis for ischaemic aetiology** included randomized treatment, region, beta-blocker use, ACE inhibitor use, mineralocorticoid receptor antagonist use, ejection fraction, presence of implanted cardioverter defibrillator or cardiac resynchronization therapy, NYHA class, hypertension, diabetes, past hospitalization for heart failure, log transformed NT-ProBNP

†**Adjusted analysis for ICD/CRT-D at baseline** included randomized treatment, region, beta-blocker use, ACE inhibitor use, mineralocorticoid receptor antagonist, ejection fraction, ischaemic aetiology, NYHA class, hypertension, diabetes, past hospitalization for heart failure, log transformed NT-ProBNP

Figure 1. Incidence of adjudicated fatal events and resuscitated cardiac arrest in patients with a reported ventricular arrhythmia



*n = 1 had a previous resuscitated cardiac arrest
**Other CV death is death from a cardiovascular cause not ascribed to sudden death or HF death
⁺n = 1 had a resuscitated cardiac arrest on the same day
§n = 1 had a previous resuscitated cardiac arrest and did not die later
#n = 2 had a resuscitated cardiac arrest before the VA event
^n = 2 had a resuscitated cardiac arrest after the VA event
>n = 1 had a resuscitated cardiac arrest before the VA event
<n = 2 also a resuscitated cardiac arrest after the VA event

Figure 2. Kaplan Meier curves for time to first ventricular arrhythmia according to treatment assignment

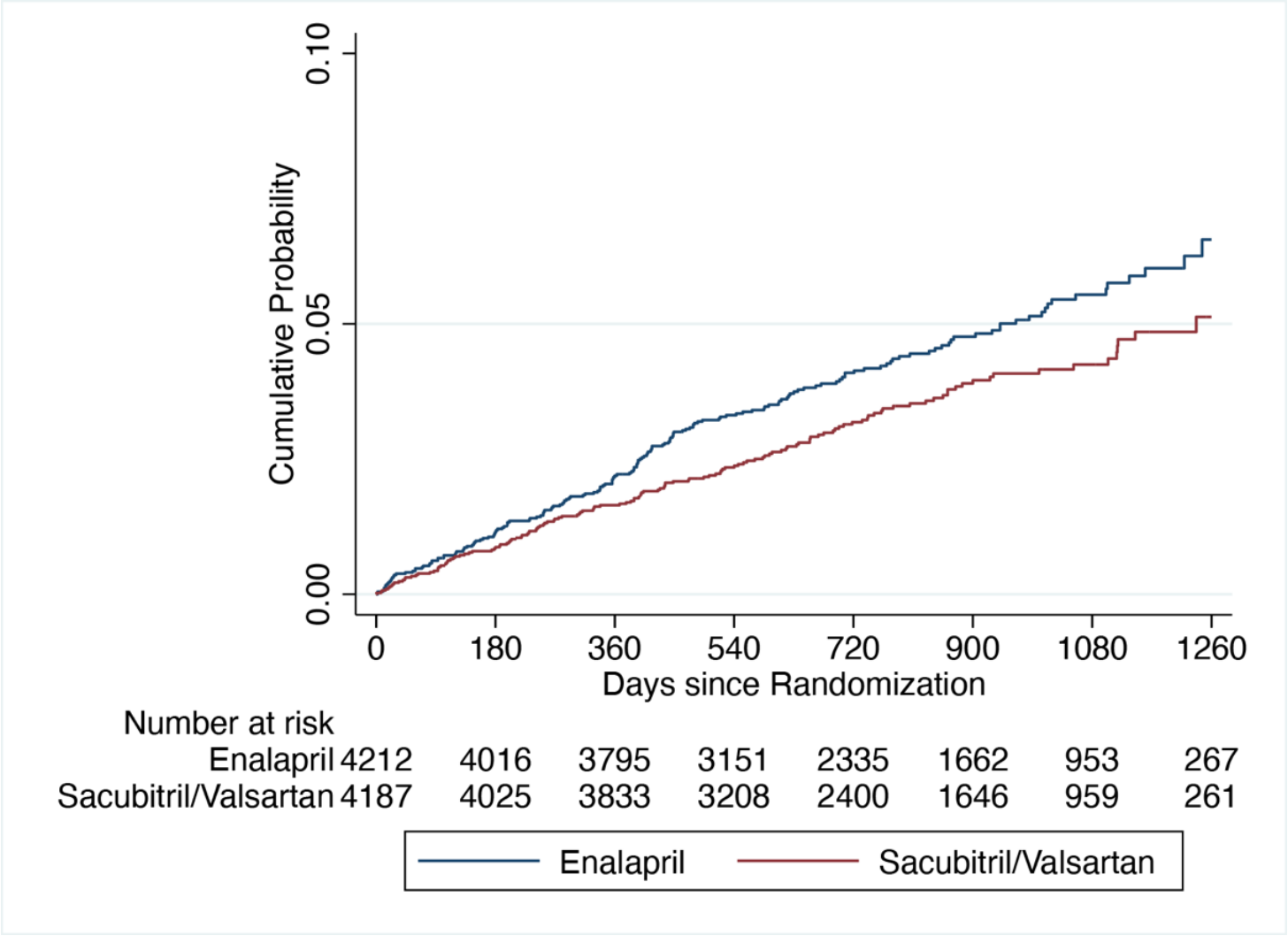


Figure 3. Kaplan Meier curves for time to first ventricular arrhythmia / ICD shock / resuscitated cardiac arrest according to treatment assignment