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Early and late ventricular arrhythmias complicating ST-segment elevation myocardial infarction

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ABSTRACT

Background: Ventricular arrhythmias (VA) can be life-threatening complications of ST-segment elevation myocardial infarction (STEMI).

Aims: We aimed at describing the incidence, predictors, and in-hospital impact of early VA (EVA, occurring < day 2 post-STEMI) and late VA (LVA, occurring ≥ day 2 post-STEMI) in STEMI patients.

Methods: Data of 13523 patients enrolled in a prospective registry were analyzed. Logistic and Cox regressions were performed to identify predictors of EVA, LVA, and in-hospital all-cause mortality. Predictors of LVA were used to build a risk score.

Results EVA occurred in 678 patients (5%) whereas 120 patients (0.9%) experienced LVA at a median timing of 3 days post-STEMI. EVA associated with a significantly higher risk of all-cause mortality (HR: 1.44, 95%CI: 1.17-1.76, p<0.001) whereas no association was observed with LVA (HR: 0.86, 95%CI: 0.57-1.28, p=0.45). Multivariable predictors of LVA were : age ≥ 65 years old, serum creatinine ≥ 85 μmol/l on admission, pulse pressure ≤ 45 mmHg on admission, presence of a Q wave on admission ECG, post-percutaneous coronary intervention TIMI flow grade < 3, and left ventricular ejection fraction≤ 45%.The score derived from these variables allowed the classification of patients into four risk categories: low (0–21), low-to- intermediate (22–34), intermediate-to-high (35–44), and high (≥45). Observed LVA rates were 0.2%, 0.3%, 0.9%, and 2.5%, across the four risk categories, respectively. The model demonstrated good discrimination (20-fold cross-validated c-statistic of 0.76) and adequate calibration (Hosmer-Lemeshow p=0.23).

Conclusion: EVA is 5-fold more common than LVA in the setting of STEMI and portends a higher risk of in-hospital all-cause mortality. LVA is mainly associated with patients baseline risk profile and surrogate markers of larger infarct size. We developed and internally validated a risk score identifying patients at high risk of LVA for whom early intensive care unit discharge may not be suitable.

Keywords: ST-segment elevation myocardial infarction, ventricular arrhythmia, prognosis, risk score.

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RESUME

Contexte: Les arythmies ventriculaires (AV) peuvent représenter des complications mortelles des syndromes coronariens aigus avec sus-décalage du segment ST (SCA ST+).

Objectifs: Décrire l'incidence, les facteurs prédictifs et le prognostic hospitalier des AV précoces (AVP, survenant < 2 jours après le SCA ST+) et tardives (AVT, survenant < 2 jours après le SCA ST+).

Methods: Les données de 13523 patients inclus dans un registre prospectif ont été utilisées. Des regressions logistiques et de Cox ont été utilisées pour identifier les facteurs prédictifs d'AVP, AVT et mortalité hospitalière. Un score de risqué d'AVT a été créé à partir des facteurs prédictifs identifiés.

Results: Une AVP est survenue chez 687 patients (5%) alors que 120 patients (0.9%) ont présenté une AVT à un délai median de 3 jours post-SCA ST+. Les arythmies précoces étaient associées à un risque accru de mortalité hospitalière (HR: 1.44, IC95%: 1.17-1.76, p<0.001) contrairement aux AVT (HR: 0.86, IC95%: 0.57-1.28, p=0.45). Les facteurs prédictifs multivariés d'AVT étaients: un age ≥ 65 years old, une créatininémie ≥ 85 μmol/l à l'admission, une pression pulsée ≤ 45 mmHg à l'admission, une onde Q sur l'ECG d'admission, un flux TIMI< 3 après angioplastie et une fraction d'éjection du ventricule gauche≤ 45%. Le score établi à partir de ces variables a permis la classification des patients en 4 groupes de risque: bas (0–21), bas à intermédiaire (22–34), intermédiaire à haut (35–44), and haut (≥45). Les taux d'AVT observes au sein de ces 4 catégories étaient respectivement de 0.2%, 0.3%, 0.9%, et 2.5%. Le modèle a démontré une discrimination (c-statistic après validation croisée sur 20 échantillons de 0.76) et une calibration adéquates (p de Hosmer-Lemeshow=0.23).

Conclusion: Les AVP sont 5 fois plus fréquentes que les AVT en post-SCA ST+ et s'associent à un haut risqué de mortalité hospitalière. Les AVT sont principalement liées au profil de risque des patients et à des marqueurs de la taille de l'infarctus. Nous avons développé et réalisé la validation interne d'un score de risqué identifiant les patients à haut risque d'AVT pour lesquels une sortie précoce d'une unité de soins intensifs pourrait ne pas être souhaitable.

Mots-clés : Syndrome coronarien aigu avec sus-décalage du segment ST ; arythmies ventriculaires, pronostic, score de risque.

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LIST OF ABBREVIATIONS

FMC: first medical contact

ICU: intensive care unit

LVEF: left ventricular ejection fraction

MACE: major adverse cardiac events

PPCI: primary percutaneous coronary intervention

STEMI: ST-segment elevation myocardial infarction

TIMI: Thrombolysis In Myocardial Infarction

VA: ventricular arrhythmia

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BACKGROUND

Ventricular arrhythmias (VA), including sustained ventricular tachycardia and ventricular fibrillation are a frequent complication of ST-segment elevation myocardial infarction (STEMI), justifying a continuous ECG monitoring for at least 24h after symptom onset in all STEMI patients [1]. Despite a reduction in the incidence of VA in STEMI cases in the primary percutaneous coronary intervention (PPCI) era, approximately 6-10% of STEMI patients still develop significant VA [2]. VA *per se* may be a cause of increased STEMI mortality, and are directly linked to 2-4 % 30-day cardiac mortality in some studies [3,4].

Mechanisms in the genesis of VA have been well identified, including automaticity, triggered activity and re-entry. Ischemia and reperfusion induce precipitating factors ranging from ionic disturbances, secretion of catecholamine to volume overload. These factors and their influence can vary over time after the onset of STEMI and revascularization [5]. Therefore, many studies have separated VA in different categories of timing after STEMI and PPCI, demonstrating that timing of occurrence of VA influences their incidence, risk factors and clinical significance. Overall, the majority of VA occurs early (EVA) within 24-48h of symptom onset. However a sizeable proportion of VA occurs after this cut-off, and a recent study suggests that these late VA (LVA) portend a poorer prognosis with higher in-hospital mortality [6,7]. Specialized units such as cardiac intensive care units (ICU) or coronary care units represent the ideal setting to treat VA in an optimal and timely manner. The length of ICU stay has been progressively reduced over time owing to earlier revascularization. Current guidelines recommend that the length of ICU stay and ECG monitoring should be determined on an individual basis[1]. Thus, it is crucial to identify risk factors for LVA, which would help to distinguish patients who may benefit from a longer surveillance in the ICU. Nonetheless, there is no formal definition of LVA, and the largest reports defined it as any VA occurring after the cardiac catheterization, which may not be the most clinically relevant cut-off [8–10].

Using a large prospective multicenter registry of STEMI patients (Observatoire Régional Breton sur l'Infarctus, ORBI), we sought to determine the in-hospital incidence, mortality and risk factors for EVA and LVA, as well as to derive and internally validate a risk score to identify patients at high-risk of LVA.

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METHODS

The ORBI Registry

This observational study used data from the Brittany Regional Infarction Observatory (Observatoire Régional Breton sur l'Infarctus, ORBI) that prospectively includes all patients admitted since 2006 to any of the 9 participating interventional cardiology centers located in Brittany, France, for STEMI (final diagnosis), within 24h of symptom onset. Demographic data, patient medical background, hemodynamic status, pre- and in-hospital delays before medical care and PPCI, treatments, procedural characteristics and in-hospital outcomes were collected in a dedicated database [11,12]. This registry was approved by the Commission Nationale de l'Informatique et des Libertés, and the study protocol was approved by the local ethics committee.

Patients

Patients enrolled in the ORBI registry between June 2006 and June 2019 were analyzed. Patients with available data on the occurrence and timing of VA were included. They were separated in three groups: no VA, EVA and LVA.

Definitions

STEMI was defined according to the universal definition of myocardial infarction as ST segment elevation, measured at the J point, ≥1 mm in two contiguous leads or new left bundle branch block, accompanied by one or more positive cardiac biomarkers confirming cardiac necrosis [13]. VA was defined as the occurrence of a sustained ventricular tachycardia with a duration > 30 seconds or ventricular fibrillation documented by ECG or cardiac monitoring. Early VA were defined as any VA occurring the day of symptom onset or the next day (day 0 or 1), including before and during PPCI, while LVA were defined as VA occurring between day 2 and discharge. Early complications were defined as occurring the day of symptoms onset or the next day. First medical contact (FMC) was defined according to the 2008 European Society of Cardiology STEMI guidelines [14]. Total ischemic time and FMC-to-treatment delay were defined as the time between symptom onset and FMC, and initiation of reperfusion: balloon inflation or thromboaspiration in the case of PPCI or administration of

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the fibrinolytic treatment in case of fibrinolysis, respectively. Mechanical circulatory assistances included intra-aortic balloon pump, extra corporeal membrane oxygenation and the Impella left ventricular assist device (Abiomed, Danvers, MA). Mechanical complication was defined as the occurrence of either ischemic mitral regurgitation or ventricular septal rupture. High-degree atrioventricular block was defined as third or second-degree type 2 atrioventricular blocks.

Outcomes

The primary outcome was the occurrence and timing of sustained VA as previously defined. Secondary outcomes included in-hospital major adverse cardiac events (MACE) defined as the composite of all-cause mortality, non-fatal myocardial infarction, stent thrombosis, and stroke, all-cause death and individual STEMI complications. Predictors of VA according to their timing of occurrence were analyzed. The impact of VA upon in-hospital mortality was also assessed.

Statistical Analysis

Data are summarized as number (percentages) for categorical variables. Continuous variables are expressed as median (interquartile range). Qualitative data were compared using the $\chi 2$ or Fisher exact tests while continuous data were compared using the Mann–Whitney U test. All tests were 2-sided at the 0.05 significance level. Kaplan–Meier time-to-event curves were used to analyze in-hospital mortality according to VA and their timing. Univariable and multivariable Cox regression was performed to identify independent predictors of in-hospital mortality. Predictors of EVA and LVA were evaluated using univariable and multivariable logistic regression. All univariable analyses were performed on complete cases. Overall, 1.47% of data in candidate variables for multivariable analysis were missing and a total of 35.3% of patients had at least 1 missing value. For the purposes of multivariable analysis, assuming missing data were randomly missing, multiple imputation using Monte Carlo Markov Chained equations was used to generate 10 datasets without missing values. Results of multivariable analyses were combined using Rubin's rule [15]. In each model, variables with a *P*-value <0.10 in univariable analysis were entered in the multivariable analysis. To derive a simple and readily-useable risk score identifying patients at high-risk of LVA, receiver-operator curves were used to

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categorize continuous variables with a univariable p-value <0.10 by selecting clinically-relevant cut-offs, which were the closest to the optimal cut-off according to the Youden's index. A stepwise process was applied to identify the best parsimonious set of predictors. A 1000-fold bootstrap resampling was performed to calculate a shrinkage factor which was applied as a multiplier to regression coefficients of the final model to avoid overfitting to the development data [16]. These corrected coefficients of significant multivariable predictors ($p<0.05$) were then divided by the lowest coefficient value in the model, multiplied by 10 and rounded to the nearest integer to assign a risk score weight to each predictor in the model. Each patient's risk score was calculated by adding these weights. An objective assessment of calibration was obtained by performing the Hosmer–Lemeshow goodness-of-fit test and by plotting observed vs. predicted incidence rate across deciles of risk score. The predictive performance of the risk score was assessed by the c-statistic which was 20-fold cross-validated to evaluate the expected decrease in discriminative ability among new patients[16]. Multicollinearity between the variables in each model was assessed by calculation of the variance inflation factor and the tolerance. Statistical analysis was performed with the use of Statistical Package for Social Sciences version 25 (SPSS, Chicago, IL, USA) and Stata Statistical Software release 13 (StataCorp, LLC, College Station, TX, USA).

RESULTS

From June 2006 to June 2019, a total of 13 573 patients were included in the ORBI registry, among whom 13 523 (mean age: 62,1 ± 10.0, male : 77 %) had available data regarding the occurrence and timing of VA and were included in this study. Overall, 5.9% of the patients (n=798) had VA recorded during their hospital stay, 678 (85%) were classified as EVA patients and 120 (15%) were classified as LVA patients, the latter presenting VA at a median of 3 days post-STEMI. **Figure 1** shows the daily number of patients with LVA according to time from symptom onset. Among EVA patients, 285 (42.0%) presented sustained ventricular tachycardia compared with 97 (80.8%) patients with LVA ($p<0.001$). Conversely, 440 EVA patients (64.9%) and 37 of their LVA counterparts (30.8%) presented ventricular fibrillation ($p<0.001$).

Baseline characteristics of patients according to the occurrence of VA are presented in **Table 1**. Compared with patients without VA, patients developing VA during their hospital stay had signs of

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poorer hemodynamic status on admission with a higher rate of Killip class III or IV heart failure, lower blood pressure, and higher creatinine level. Patients in the LVA group were significantly older than in the EVA group. Total ischemic time was significantly longer in the LVA group compared to the EVA group, and the rate of Q wave on the admission ECG was higher in the LVA group.

There were significant differences in the acute phase management between the no VA, EVA or LVA group (**Table 2**). Patients developing VA were more likely to have a left main coronary artery lesion, whether culprit or not, and an impaired flow in the culprit artery at the time of PPCI (pre-PPCI Thrombolysis In Myocardial Infarction (TIMI) flow grade 3: 13.5% and 12.8% for EVA and LVA groups, respectively vs. 24.2% for the no VA group, p<0.001).

Supplemental table 1 summarizes in-hospital management. Patients with EVA or LVA were more likely to require a temporary pacemaker, mechanical circulatory assistance, or mechanical ventilation. They also had a significantly lower left ventricular ejection fraction (LVEF), and were less likely to receive most guidelines-recommended therapies within 48h of admission.

In-hospital outcomes

VA were associated with an increased risk of in-hospital MACE (24.6% and 23.3% for EVA and LVA, respectively vs 5.6% for no VA, p<0.001), all-cause mortality (20.2% for EVA and 22.5% for LVA vs. 4.1% for no VA, p<0.001)(**Figure 2**), as well as most individual STEMI complications (**Table 3**). Compared to EVA, LVA were associated with higher rates of Killip III/IV heart failure development (27% vs 15.3%), and mechanical complications (10.0% vs. 3.5%) and with a longer length of stay in ICU and the hospital.

Predictors of early VA

Table 4 summarizes the predictors of EVA. Covariates independently associated with an increased EVA included a higher glycaemia on admission, a shorter symptoms-to-first medical contact delay, a lower pulse pressure, a depressed LVEF, the presence of Killip class III or IV heart failure on admission, the occurrence of certain early complications of STEMI or the early need for additional techniques to treat these complications. Among these complications, the occurrence of early stent

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thrombosis was the strongest predictor of EVA (odds-ratio: 4.15, 95% confidence interval: 2.35-7.33, p<0.001).

Predictors of late VA

Univariable and multivariable predictors of LVA are listed in **supplemental Table 2**. Seven predictors were independently associated with LVA in multivariable analysis: age ≥ 65 years old, serum creatinine ≥ 85 µmol/l (0.97mg/dl) on admission, pulse pressure ≤ 45 mmHg on admission, presence of a Q wave on admission ECG, post-PCI TIMI flow grade < 3, and LVEF ≤ 45%. The c-statistic of the final model was 0.78 (95% CI: 0.73-0.84) showing fair discrimination. Cross-validation predicted a very slight decrease in discriminative ability (c-statistic: 0.76, 95% CI: 0.72-0.82). The p-value of the Hosmer-Lemeshow goodness-of-fit test was 0.23.

Late VA risk score building

Points assigned to each variable of the risk-scoring system were derived from the regression coefficients of the final multivariable model (**Figure 3**). The score was calculated by adding each component and theoretically ranged from 0 to 90. The relationship between the score value and the predicted incidence of in-hospital CS is shown in **supplemental Figure 1**. **Supplemental Figure 2** illustrates the calibration plot of predicted vs. observed incidence of LVA in the population study across deciles of risk score confirming an adequate calibration. Levels of risk were defined according to the predicted incidence of LVA: low-risk for a score ≤ 21 corresponding to a predicted incidence ≤0.27% (median: 0.15%), low-to-intermediate risk for a score ≥ 23 and ≤ 34 corresponding to a predicted incidence >0.27% and ≤0.58% (median: 0.38%), intermediate-to-high risk for a score ≥ 35 and ≤ 44 corresponding to a predicted incidence >0.58% and ≤1.06% (median: 0.83%), and high risk for a score ≥ 45 corresponding to a predicted incidence >1.06% (median: 1.92%). Observed incidences of LVA according to these risk groups were: 0.2%, 0,3%, 0.9%, and 2.5%.

Predictors of in-hospital mortality

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Univariable and multivariable predictors of in-hospital mortality are listed in **Table 5**. Early VA was independently associated with increased in-hospital mortality (hazard ratio: 1.44, 95% confidence interval: 1.17-1.76, p=0.001) whereas LVA *per se* was not a risk factor of in-hospital death (hazard ratio: 0.86, 95% confidence interval: 0.57-1.28 ; p= 0.45) (**Figure 2**).

DISCUSSION

To the best of our knowledge, the present study involves the largest cohort of STEMI patients in the PPCI era with a focus on VA incidence, timing and predictors. Among 13523 patients, VA occurred in 798 patients (5.9%), among whom 120 (0.9%) developed LVA at or beyond day 2 after symptom onset. Early VA were approximately 5-fold more common than LVA and associated with an increased risk of in-hospital mortality. Predictors of EVA were mainly related to a poorer hemodynamic status on admission, a larger infarct size, and several early STEMI complications or interventions required to treat these complications. Early stent thrombosis was the strongest predictor of EVA. On the contrary, LVA were not related to these early complications but rather associated with the baseline risk profile of patients (older age, renal function, poorer hemodynamics) and infarct size (Q-wave on admission, post-PPCI TIMI flow grade < 3, depressed LVEF). The risk score derived from these predictors enabled adequate identification of patients at high risk of LVA. Although LVA was not associated with increased in-hospital mortality in the present study, such a risk score may be valuable in routine clinical practice to identify patients for whom early ICU discharge or a shorter continuous ECG monitoring period may not be suitable.

Late VA definitions

In previous studies various definitions of LVA have been adopted. In a Pexelizumab in Conjunction With Angioplasty in Acute Myocardial Infarction (APEX-AMI) substudy encompassing 5745 STEMI patients enrolled between 2004 and 2006, LVA was defined as any sustained ventricular tachycardia/fibrillation occurring after the cardiac catheterization [8]. The same definition was applied in the Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) substudy focusing on VA, which included 3,485 patients undergoing PPCI, and by

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Huang et al in their recent retrospective study of 607 STEMI patients [9]. Another study chose to define late VA as occurring more than one hour after cardiac catheterization [17]. In the present study, the cut-off of day 2 post-symptom onset used to define LVA was chosen for its clinical relevance since identifying patients at higher risk of VA beyond this cut-off can justify a delayed discharge from ICU and prolonged ECG monitoring. A comparable definition was used by Tran et al. in their evaluation of 25 years trends of incidence and case-fatality rate of VA complicating acute myocardial infarction in central Massachusetts [18] as well as by Takada et al [7].

VA Incidence

Although incidence of significant VA in patients hospitalized for STEMI has been decreasing over the past decades akin to other STEMI complications owing to improvements in reperfusion therapies performance and timeliness, it remains a common and possibly life-threatening complication [10]. Tran et al reported that the hospital incidence of ventricular tachycardia declined from 14.3% in 1986/1988 to 10.5% in 2009/2011 and from 8.2% to 1.7% for ventricular fibrillation [18]. The definition of ventricular tachycardia as any cardiac arrhythmia of ≥ 3 consecutive complexes originating in the ventricles at a rate of greater than 100 beats/min used in this study likely explain the higher observed incidence rates compared with other recent studies. Overall VA incidence in our study was 5.9%, in line with the APEX-AMI substudy, which demonstrated an incidence of 5.7% across 5745 patients enrolled at 296 centers in 17 countries [8]. It also showed that incidence of VA differs depending on the timing in relation to reperfusion: pre-reperfusion VA were more frequent than reperfusion-induced, early post-reperfusion or late post-reperfusion VA [8]. Similarly in our study, the occurrence of LVA decreased exponentially with time from symptoms onset with a median delay of 3 days (**Figure 1**).

Predictors of VA

Previous studies sought to determine predictors of VA in patients hospitalized for STEMI, although with smaller cohorts [8,10,17,19]. Some predictors were similar to those found in the present study, particularly surrogate markers of a larger infarct size or heart failure such as a low systolic blood pressure, a higher heart rate, or a lower left ventricular ejection fraction. In a substudy based on the

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HORIZONS-AMI trial population, Mehta et al found that the stronger predictors of VA were a Killip class higher than I and a thrombotic culprit lesion at baseline [9]. Unlike previous studies, patients' cardiovascular risk factors were not predictive of VA in the present study. However, although its relation with the risk of post-STEMI VA is complex, involving elevated sympathetic activity and acute inflammatory processes [20], a higher glycaemia on admission, which may suggest unknown diabetes mellitus at the time of admission in some patients, was associated with EVA in the present study. In addition to those predictors, the APEX-AMI substudy showed a higher risk associated with inferior STEMI compared to other territories [8]. The association of VA with right coronary artery-related infarct was also reported by Metha et al in 3065 patients enrolled in the Primary Angioplasty in Myocardial Infarction (PAMI) study [10]. We can hypothesize that inferior MI and right coronary artery-related infarct would have a higher rate of right ventricular dysfunction for which introduction of beta-blockers might be delayed, thus increasing the risk of VA occurrence.

Compared to LVA, EVA were more likely to present as a ventricular fibrillation (64.9% vs 30.8%), whereas LVA were more often presenting as ventricular tachycardia. We also showed that the strongest predictor of EVA was early stent thrombosis among other early STEMI complications, whereas predictors of LVA were related to infarct size and heart failure. These findings suggest that aside from common approaches to mitigate the risk of VA, such as avoidance of ionic disturbances and volume overload as well as proper left ventricular support and unloading when appropriate, the risk of EVA might be further reduced by preventing early stent thrombosis through optimized anti-thrombotic regimen, careful stent deployment and even, in some cases, delayed stent implantation in a thrombus-laden culprit lesion.

Impact of VA

In our study, EVA were associated with an increased in-hospital mortality, in line with previous studies. For instance, Masuda et al found an increased in-hospital mortality rate of 14.6% in patients with VA compared with 4.3% among patients without VA [6]. Similarly, VA were associated with a more than 3-fold higher 90-day mortality after adjustment for confounders in the APEX-AMI substudy [8]. On the contrary, VA did not influence in-hospital and 1-year mortality in the PAMI substudy [10].

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Interestingly, LVA were not independently associated with increased in-hospital mortality in our study. It can be hypothesized that LVA associating with surrogate markers of larger infarct size might just be a “bystander” of more severe STEMI cases portending poorer short and long-term prognosis. Another possible explanation to this finding could be the fact that patients admitted for STEMI were seldom discharged from ICU within 48 hours of symptoms onset in centers participating in the ORBI registry over the study period, which may have contributed to reduce the impact of LVA upon in-hospital outcomes. Therefore, our findings may not be generalizable to centers routinely performing an early discharge from ICU. The risk score derived in the present study may provide a valuable tool to identify high-risk patients who may not be suitable for such an early discharge strategy.

Limitations

Retrospective observational studies are inherently vulnerable to selection bias and unidentified confounders, thus our study has some limitations that need to be acknowledged. Firstly, as in any registry, under-reporting of complications, even clinically significant ones such as VA cannot be ruled out. Moreover, the ORBI registry is restricted to patients admitted to an interventional cardiology center, which may induce selection bias: STEMI cases managed medically in non-interventional centers or patients who do not survive the prehospital phase are not enrolled. Another limitation of this study is the absence of certain biological parameters of importance in VA incidence such as blood potassium levels, which were not available for testing in our database. Furthermore, the LVA risk score derived from this cohort requires external validation in future studies. Finally, ORBI is limited to the in-hospital phase and does not include a long-term follow-up. Consequently, we were unable to assess the long-term prognostic significance of VA.

CONCLUSION

In a contemporary cohort of STEMI patients, VA remain a common complication affecting approximately 5% of patients. Early VA portend an increased risk of in-hospital mortality. VA occurrence diminishes with time from STEMI, but a significant number of VA (15% of all VA) occurs

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at or beyond 2 days of symptom onset. The risk score derived in this study can help identify patients exposed to a higher risk of LVA who stand to benefit the most from tailored strategies of management and monitoring.

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FIGURES LEGENDS

Figure 1: Number of patients who developed late VA according to time after admission for STEMI.
STEMI: ST-segment elevation myocardial infarction; VA: Ventricular Arrhythmias.

Figure 2: Kaplan Meier time-to-event curves showing cumulative rates of in-hospital all-cause mortality according to the occurrence and timing of ventricular arrhythmias
Time when subjects become at risk was set as admission for ST-segment elevation myocardial infarction for patients without VA and date of VA for other patients. VA: Ventricular Arrhythmias.

Figure 3: Multivariable predictors of late ventricular arrhythmias and their respective weights in the late ventricular arrhythmias predictive score.
OR: Odds-ratio; PCI: percutaneous coronary intervention; TIMI: Thrombolysis In Myocardial Infarction

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Table 1 – Baseline characteristics of the study population according to the occurrence and timing of sustained ventricular arrhythmias

Characteristics	No sustained VA (n=12725)	Early sustained VA (n=678)	Late sustained VA (n=120)	p-value
Clinical characteristics				
Age, years	62.0 (53.0-73.0)	62.0 (52.0-73.0)	72.0 (60.0-81.0)	<0.001†‡
Male sex	9887 (77.7)	512 (75.5)	93 (77.5)	0.41
Body mass index, kg/m²	26.0 (24.0-29.0), n=12396	26.0 (24.0-29.0), n=633	26.0 (24.0-29.0), n=115	0.61
Familial history of coronary artery disease	3188/12422 (25.7)	147/652 (22.5)	20/115 (17.4)	0.03
Hypertension	5095/12695 (40.1)	282/674 (41.8)	52/120 (43.3)	0.53
Diabetes mellitus	1282/12615 (10.2)	58/672 (8.6)	14/119 (11.8)	0.37
Dyslipidemia	5251/12357 (42.5)	271/656 (41.3)	54/119 (45.4)	0.68
Current smoker	4910/12643 (38.8)	274/668 (41.0)	46/119 (38.7)	0.53
Previous myocardial infarction	1025/12697 (8.1)	63/676 (9.3)	10/120 (8.3)	0.51
Previous coronary artery bypass graft	161/12699 (1.3)	7/676 (1.0)	1/120 (0.8)	0.91
Previous percutaneous coronary intervention	1187/12694 (9.4)	64/674 (9.5)	13/120 (10.8)	0.85
Chronic obstructive pulmonary disease	624/12689 (4.9)	39/673 (5.8)	11/120 (9.2)	0.07
Previous stroke/transient ischemic attack	475/12692 (3.7)	22/673 (3.3)	9/120 (7.5)	0.09
Peripheral artery disease	527/12689 (4.2)	36/673 (5.3)	10/120 (8.3)	0.03
Permanent pacemaker	83/12690 (0.7)	5/673 (0.7)	1/120 (0.8)	0.94
Presentation				
Presentation as cardiac arrest	345/12458 (2.8)	65/665 (9.8)	6/119 (5.0)	<0.001*
Admission to a non-PCI capable center	2619 (20.6)	130 (19.2)	23 (19.2)	0.63
Managed by mobile intensive care unit	7644 (60.1)	424 (62.5)	74 (61.7)	0.42
Treatment delays, min				
Symptoms-to-first medical contact delay	97 (55-192), n=11655	75 (40-175), n=641	120 (60-210), n=109	<0.001*‡
First medical contact-to-treatment delay	93 (72-130), n=10764	95 (73-130), n=601	119 (82-153), n=97	0.007†‡
Symptoms-to-treatment delay	205 (146-321), n=10784	183 (140-270), n=578	223 (163-335), n=95	<0.001*‡
ECG on admission				
Q wave	3724/12663 (29.4)	201/669 (30.0)	58/119 (48.7)	<0.001†‡
Left bundle branch block	275/12660 (2.2)	27/675 (4.0)	2/120 (1.7)	0.01*
Anterior myocardial infarction	5221 (41.0)	297 (43.8)	56 (46.7)	0.17
Hemodynamic on admission				
Killip class III or IV	579/12656 (4.6)	135/664 (20.3)	16/118 (13.6)	<0.001*†
Heart rate, b.p.m	75 (64-87), n=12355	77 (63-90), n=640	83 (70-99), n=115	<0.001†‡
Systolic blood pressure, mmHg	133 (117-150), n=12460	120 (100-141), n=643	120 (107-140), n= 114	<0.001*†

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Pulse pressure, mmHg	51 (40-66), n=12431	44 (33-56), n=640	43 (35-56), n=113	<0.001*†
Blood tests on admission				
Serum creatinine level, µmol/l	80 (68-93), n=12460	86 (72-104), n=651	91 (73-114), n=118	<0.001*†
Glomerular filtration rate (MDRD), ml/min/1.73m²	87 (71-103), n=12460	_80 (62-98), n=651	73 (54-95), n=118	<0.001*†
Glycemia, mmol/l	7.3 (6.2-9.0), n=11896	8.7 (6.9-11.5), n=603	8.6 (7.0-11.0), n=112	<0.001*†

* Denotes a significant Bonferroni-corrected post-hoc pairwise comparison between the no sustained VA and the early sustained VA groups

† Denotes a significant Bonferroni-corrected post-hoc pairwise comparison between the no sustained VA and the late sustained VA groups

‡ Denotes a significant Bonferroni-corrected post-hoc pairwise comparison between the early sustained VA and the late sustained VA groups

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Table 2 – Acute phase management and angiographic findings of the study population according to the occurrence and timing of sustained ventricular arrhythmias

Characteristics	No sustained VA (n=12725)	Early sustained VA (n=678)	Late sustained VA (n=120)	p-value
Acute management strategy				
Primary percutaneous coronary intervention	10101 (79.4)	561 (82.7)	100 (83.3)	0.011*
Fibrinolysis	1134 (8.9)	70 (10.3)	5 (4.2)	
Secondary percutaneous coronary intervention	437 (3.4)	12 (1.8)	5 (4.2)	
Coronary angiogram – No Revascularization	885 (7.0)	27 (4.0)	8 (6.7)	
No coronary angiogram-No Revascularization	168 (1.3)	8 (1.2)	2 (1.7)	
Coronary angiogram				
Coronary angiogram performed	12543 (98.6)	669 (98.7)	118 (98.3)	1.00
Radial access	7907/11123 (71.1)	332/607 (54.7)	56/108 (51.9)	<0.001*†
Significant lesions				
Left anterior descending artery	8116/12446 (65.2)	447/668 (66.9)	82/118 (69.5)	0.42
Left circumflex	5036/12443 (40.5)	261/668 (39.1)	45/118 (38.1)	0.68
Right coronary artery	7233/12438 (58.2)	395/667 (59.2)	64/118 (54.2)	0.59
Left main	445/12439 (3.6)	43/668 (6.4)	11/118 (9.3)	<0.001*†
Coronary anatomy	n=12308	n=666	n=116	0.89
Single-vessel disease	6255 (50.8)	328 (49.2)	57 (49.1)	
Two-vessel disease	3762 (30.6)	206 (30.9)	35 (30.2)	
Three-vessel disease	2291 (18.6)	132 (19.8)	24 (20.7)	
Culprit lesion				
Left anterior descending artery	5207/12448 (41.8)	284/668 (42.5)	56/118 (47.5)	0.44
Left circumflex	1961/12446 (15.8)	96/668 (14.4)	18/118 (15.3)	0.63
Right coronary artery	5187/12446 (41.7)	274/668 (41.0)	40/118 (33.9)	0.22
Left main	101/12446 (0.8)	19/668 (2.8)	5/118 (4.2)	<0.001*†
PCI performed	11477 (90.2)	637 (94.0)	110 (91.7)	0.005*
Pre-PCI TIMI Flow grade 3	2996/12381 (24.2)	90/666 (13.5)	15/117 (12.8)	<0.001*†
Thromboaspiration	5265/11475 (45.9)	348/637 (54.6)	61/110 (55.5)	<0.001*
Glycoprotein IIb/IIIa inhibitors use	4984/12717 (39.2)	314/677 (46.4)	47/120 (39.2)	0.001*
Stent implantation	n=11411	n=632	n=106	0.002*†
No stent	890 (7.8)	74 (11.7)	13 (12.3)	
Bare-metal stent	5609 (49.2)	318 (50.3)	57 (53.8)	

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Drug-eluting stent	4912 (43.0)	240 (38.0)	36 (34.0)	
Post-PCI TIMI flow grade 3	10827/11384 (95.1)	566/630 (89.8)	83/104 (79.8)	<0.001*†‡
Complete revascularization after index procedure	5422/11459 (47.3)	289/637 (45.4)	50/110 (45.5)	0.59

PCI: percutaneous coronary intervention; TIMI: Thrombolysis In Myocardial Infarction

* Denotes a significant Bonferroni-corrected post-hoc pairwise comparison between the « No sustained VA » and « early sustained VA » groups

† Denotes a significant Bonferroni-corrected post-hoc pairwise comparison between the « No sustained VA » and « late sustained VA » groups

‡ Denotes a significant Bonferroni-corrected post-hoc pairwise comparison between the «early sustained VA» and « late sustained VA » groups

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Table 3 – In-hospital outcomes of the study population according to the occurrence and timing of sustained ventricular arrhythmias

Outcomes	No sustained VA (n=12725)	Early sustained VA (n=678)	Late sustained VA (n=120)	p-value
Major adverse cardiovascular events	710 (5.6)	167 (24.6)	28 (23.3)	<0.001*†
All-cause mortality	528 (4.1)	137 (20.2)	27 (22.5)	<0.001*†
Cardiovascular mortality	487 (3.8)	130 (19.2)	25 (20.8)	<0.001*†
Non-fatal myocardial infarction	115 (0.9)	23 (3.4)	2 (1.7)	<0.001*
Stent thrombosis	94 (0.7)	23 (3.4)	1 (0.8)	<0.001*
Stroke	62 (0.5)	10 (1.5)	0 (0.0)	0.009*
Development of Killip class III/IV heart failure	572 (4.5)	101 (15.3)	31 (27.0)	<0.001*†‡
Mechanical complications	429 (3.4)	24 (3.5)	12 (10.0)	0.003†‡
High-degree atrioventricular block	405 (3.2)	60 (8.8)	10 (8.3)	<0.001*†
New-onset atrial fibrillation/flutter	498/9593 (5.2)	52/489 (10.6)	17/90 (18.7)	<0.001*†
Right ventricular myocardial infarction	228 (1.8)	40 (5.9)	9 (7.5)	<0.001*†
Major bleeding (BARC classification 3 or 5)	191/8423 (2.3)	33/450 (7.3)	9/79 (11.4)	<0.001*†
Intensive care unit length of stay, days§	3.0 (3.0-5.0), n=12170	4.0 (3.0-6.0), n=540	6.0 (4.0-11.0), n=92	<0.001*†‡
Total hospitalization length of stay, days§	5.0 (4.0-7.0), n=12175	7.0 (5.0-10.0), n=540	11.0 (7.0-17.0), n=93	<0.001*†‡

BARC: Bleeding Academic Research Consortium

* Denotes a significant Bonferroni-corrected post-hoc pairwise comparison between the « No sustained VA » and « early sustained VA » groups

† Denotes a significant Bonferroni-corrected post-hoc pairwise comparison between the « No sustained VA » and « late sustained VA » groups

‡ Denotes a significant Bonferroni-corrected post-hoc pairwise comparison between the «early sustained VA» and « late sustained VA » groups

§Among patients discharged alive from the hospital.

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Table 4 - Predictors of early sustained ventricular arrhythmias				
Variables	**Univariable OR (95% CI)**	**p-value**	**Multivariable OR (95% CI)**	**p-value**
Familial history of coronary artery disease	0.85 (0.70-1.02)	0.08	-	-
Serum creatinine level on admission, per 1µmol/l increase	1.004 (1.002-1.006)	<0.001	-	-
Glycaemia on admission, per 1mmol/l increase	1.10 (1.08-1.12)	<0.001	1.03 (1.01-1.05)	<0.001
Symptoms-to-first medical contact delay, per 1min increase	0.999 (0.998-0.999)	<0.001	0.999 (0.998-0.999)	<0.001
Presentation as cardiac arrest	3.77 (2.86-4.98)	<0.001	-	
Killip class III or IV heart failure on admission	5.22 (4.25-6.42)	<0.001	1.51 (1.14-1.98)	0.004
Heart rate, per 1 b.p.m increase	1.009 (1.005-1.013)	<0.001	-	-
Pulse pressure, per 1mmHg increase	0.978 (0.974-0.983)	<0.001	0.991 (0.987-0.995)	<0.001
Left bundle branch block on admission	1.88 (1.26-2.81)	0.002	-	
Culprit lesion of the left main	3.44 (2.10-5.64)	<0.001	-	
Post-PCI TIMI Flow grade <3	2.13 (1.63-2.80)	<0.001	-	
Left ventricular ejection fraction, per 1% increase	0.96 (0.95-0.97)	<0.001	0.98 (0.97-0.99)	<0.001
Early temporary pacemaker	6.90 (4.26-11.18)	<0.001	1.93 (1.05-3.55)	0.03
Early mechanical ventilation	7.26 (5.92-8.89)	<0.001	2.86 (2.20-3.70)	<0.001
Early mechanical circulatory support	5.27 (4.17-6.66)	<0.001	1.55 (1.16-2.07)	0.003
Early stent thrombosis	5.06 (2.95-8.67)	<0.001	4.15 (2.35-7.33)	<0.001
Early high-degree atrioventricular block	3.25 (2.40-4.39)	<0.001	1.61 (1.09-2.36)	0.02
Early right ventricular myocardial infarction	3.57 (2.47-5.16)	<0.001	1.98 (1.30-3.01)	0.001

OR: Odds-ratio; PCI: percutaneous coronary intervention; TIMI: Thrombolysis In Myocardial Infarction

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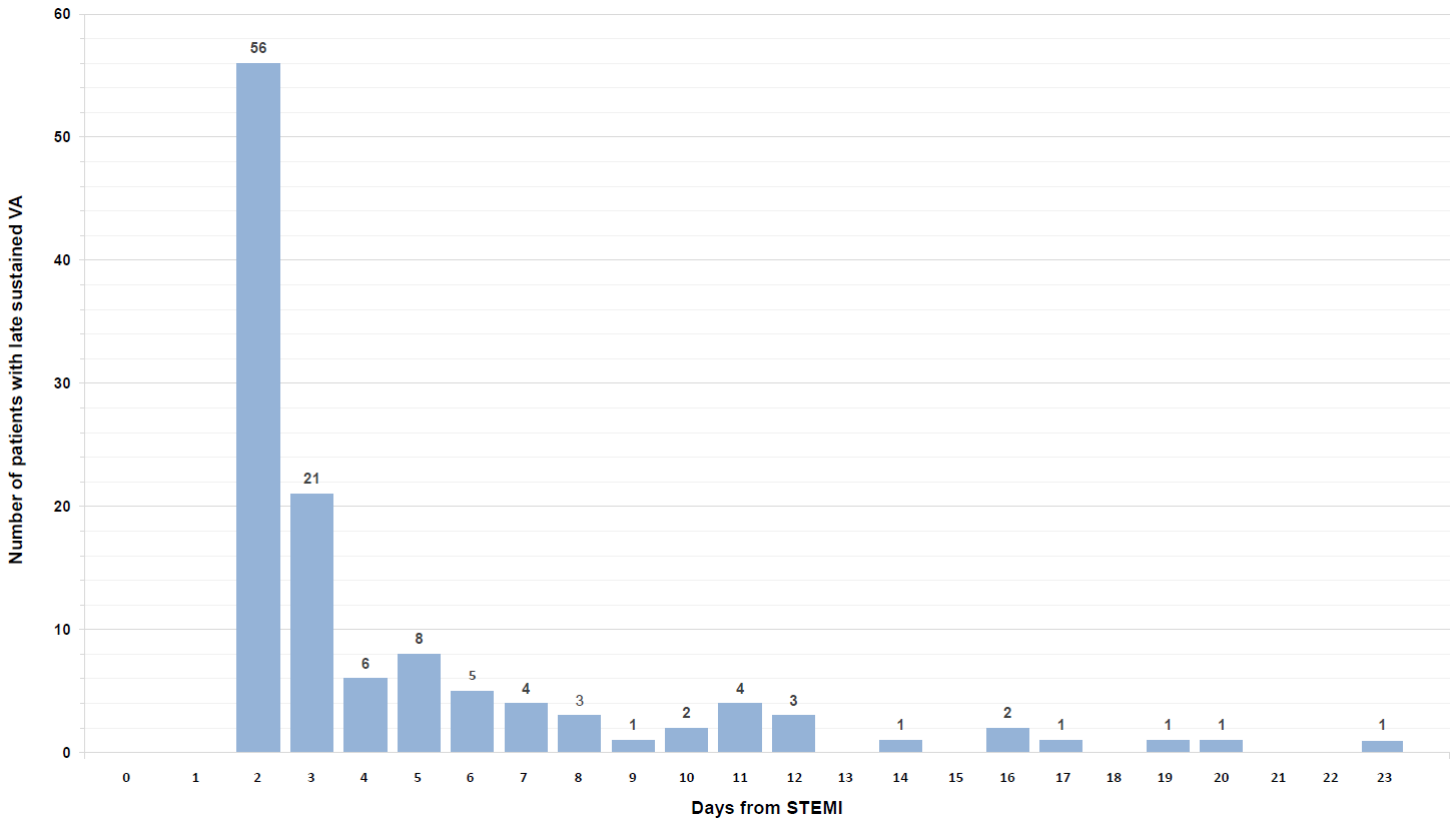
Table 5 - Predictors of in-hospital mortality				
Variables	**Univariable HR (95% CI)**	**p-value**	**Multivariable HR (95% CI)**	**p-value**
Sustained ventricular arrhythmia				
Early sustained ventricular arrhythmia	3.93 (3.25-4.77)	<0.001	1.44 (1.17-1.76)	0.001
Late sustained ventricular arrhythmia	2.87 (1.94-4.25)	<0.001	0.86 (0.57-1.28)	0.45
Age, per 1 year increase	1.05 (1.04-1.05)	<0.001	1.04 (1.03-1.05)	<0.001
Female sex	1.67 (1.43-1.95)	<0.001	1.16 (0.98-1.37)	0.08
Hypertension	1.82 (1.56-2.11)	<0.001	-	-
Diabetes mellitus	1.81 (1.48-2.20)	<0.001	-	-
Current smoker	0.56 (0.47-0.66)	<0.001	-	-
Previous myocardial infarction	1.42 (1.12-1.79)	0.004	-	-
Previous coronary artery bypass graft	2.18 (1.40-3.41)	0.001	-	-
Chronic obstructive pulmonary disease	1.50 (1.14-1.97)	0.004	-	-
Previous stroke/transient ischemic attack	1.85 (1.39-2.45)	<0.001	-	-
Peripheral artery disease	2.11 (1.65-2.70)	<0.001	-	-
Previous pacemaker	3.06 (1.80-5.20)	<0.001	-	-
Serum creatinine level on admission, per 1µmol/l increase	1.006 (1.005-1.006)	<0.001	1.004 (1.003-1.005)	<0.001
Glycemia on admission, per 1mmol/l increase	1.11 (1.10-1.11)	<0.001	1.05 (1.04-1.07)	<0.001
Presentation as cardiac arrest	5.95 (4.94-7.18)	<0.001	2.50 (2.03-3.09)	<0.001
Admission to a non-PCI capable center	0.77 (0.63-0.95)	0.014	0.80 (0.64-0.99)	0.04
Managed by mobile intensive care unit	1.40 (1.19-1.64)	<0.001	-	-
Q wave on admission	1.39 (1.19-1.62)	<0.001	1.31 (1.11-1.55)	0.002
Left bundle branch block on admission	2.73 (2.06-3.62)	<0.001	-	-
Anterior myocardial infarction	1.41 (1.22-1.64)	<0.001	-	-
Killip class III or IV heart failure	22.12 (18.43-26.56)	<0.001	4.49 (3.59-5.61)	<0.001
Heart rate, per 1 b.p.m increase	1.02 (1.01-1.02)	<0.001	-	-
Systolic blood pressure, per 1mmHg increase	0.97 (0.97-0.97)	<0.001	0.993 (0.990-0.995)	<0.001
Acute management strategy				
Primary percutaneous coronary intervention	Ref.			
Fibrinolysis	1.13 (0.86-1.48)	0.38	1.79 (1.34-2.39)	<0.001
Secondary percutaneous coronary intervention	0.38 (0.20-0.74)	0.004	0.55 (0.27-1.11)	0.10
Coronary angiogram – No Revascularization	1.24 (0.95-1.61)	0.11	1.24 (0.94-1.64)	0.12
No coronary angiogram-No Revascularization	6.43 (4.95-8.36)	<0.001	3.18 (2.38-4.23)	<0.001
Left ventricular ejection fraction, per 1% increase	0.91 (0.90-0.92)	<0.001	0.966 (0.960-0.973)	<0.001

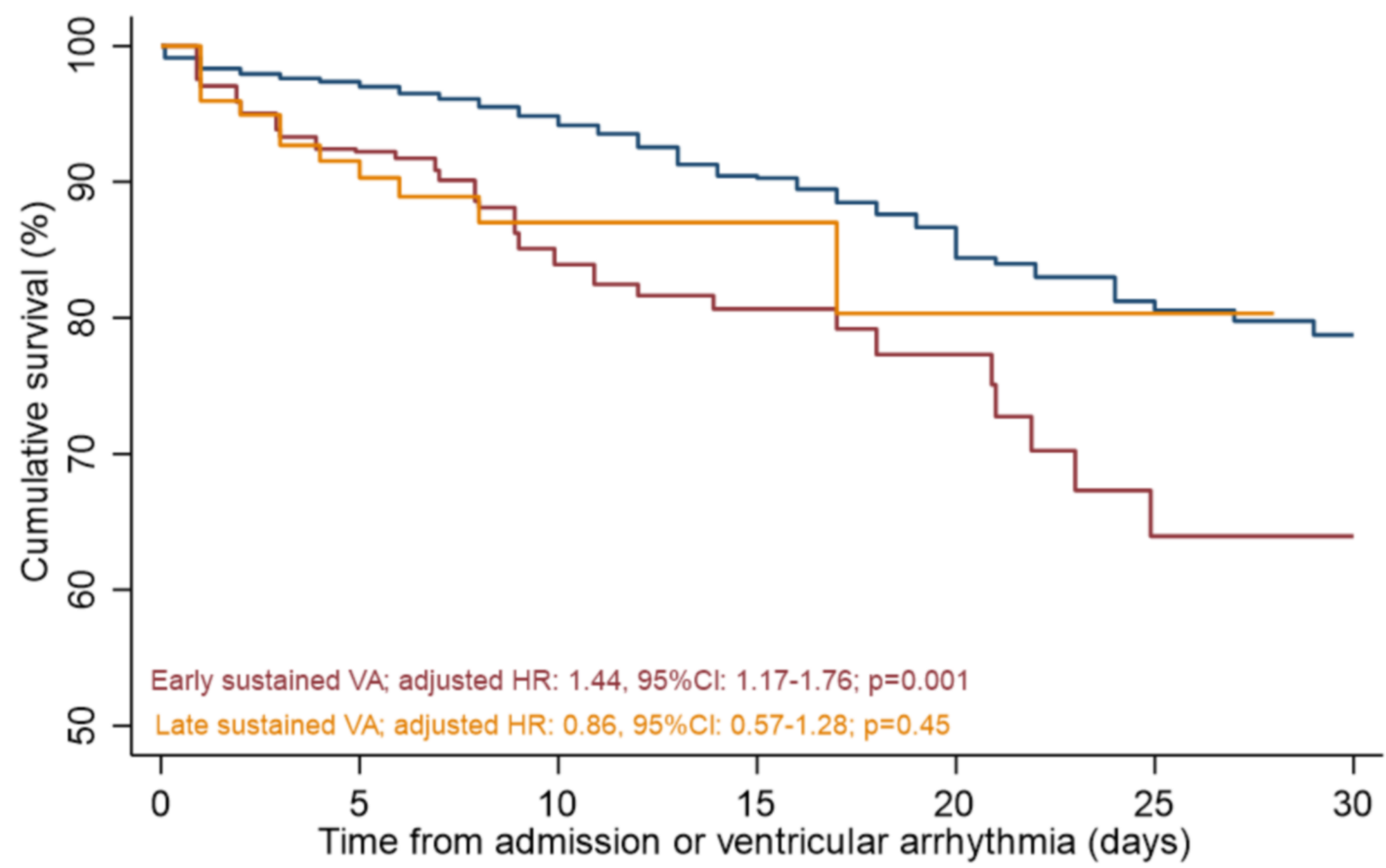
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Temporary pacemaker	3.65 (2.58-5.18)	<0.001	-	-
Mechanical ventilation	10.32 (8.80-12.10)	<0.001	1.95 (1.60-2.37)	<0.001
Mechanical circulatory support	5.36 (4.48-6.42)	<0.001	-	-
High degree atrioventricular block	2.53 (2.01-3.18)	<0.001	-	-
Mechanical complications	4.48 (3.66-5.48)	<0.001	1.96 (1.59-2.41)	<0.001
Right ventricular myocardial infarction	3.82 (2.95-4.95)	<0.001	1.61 (1.22-2.11)	0.001
Stroke	2.16 (1.33-3.48)	<0.001	-	-

PCI: percutaneous coronary intervention

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Number of patients with late sustained VA
60
50
40
30
20
10
0
56
21
6
8
5
4
3
1
2
4
3
1
2
1
1
1
1
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23
Days from STEMI



Number at risk

No VA	12725	8955	1530	551	231	121	67
Early VA	678	392	122	66	37	19	12
Late VA	120	74	32	17	10	5	3

Variable	Shrinkage factor-corrected β / Multivariable OR (95% CI)	p-value	Risk Score assigned weight
Age ≥ 65 years old	β=0.901 2.64 (1.72-4.03)	<0.001	17
Serum creatinine ≥ 85μmol/l on admission	β=0.700 2.12 (1.41-3.20)	<0.001	13
Heart rate ≥75 b.p.m on admission	β=0.538 1.78 (1.17-2.71)	0.007	10
Pulse pressure ≤ 45 mmHg on admission	β=0.568 1.84 (1.24-2.73)	0.002	11
Q wave on admission	β=0.537 1.78 (1.21-2.63)	0.004	10
Post-PCI TIMI Flow grade < 3	β=0.825 2.43 (1.47-4.02)	0.001	15
Left ventricular ejection fraction ≤ 45%	β=0.726 2.18 (1.43-3.33)	<0.001	14

