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CLINICAL RESEARCH

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

Arythmies ventriculaires précoces et tardives compliquant un infarctus du myocarde avec sus-décalage du segment ST

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Abbreviations: CI, confidence interval; ICU, intensive care unit; LVEF, left ventricular ejection fraction; ORBI, Observatoire Régional Breton sur l'Infarctus (Brittany Regional Infarction Observatory); PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction; TIMI, Thrombolysis In Myocardial Infarction; VA, ventricular arrhythmia.

☆ Tweet: Ventricular arrhythmias complicating STEMI still portend a dismal prognosis in the primary PCI era. The ORBI registry provides a risk score to identify patients at high risk of late ventricular arrhythmias.

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KEYWORDS
ST-segment elevation myocardial infarction;
Ventricular arrhythmia;
Prognosis;
Risk score

Summary
Background. — Ventricular arrhythmias can be life-threatening complications of ST-segment elevation myocardial infarction (STEMI).
Aims. — To describe the incidence, predictors and in-hospital impact of early ventricular arrhythmia (EVA, occurring < day 2 after STEMI) and late ventricular arrhythmia (LVA, occurring ≥ day 2 after STEMI) in patients with STEMI.
Methods. — Data from 13,523 patients enrolled in a prospective registry were analysed. 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 after STEMI. EVA was associated with a significantly higher risk of all-cause mortality (hazard ratio: 1.44, 95% confidence interval: 1.17—1.76; $P = 0.001$), whereas no association was observed with LVA (hazard ratio 0.86, 95% confidence interval 0.57—1.28; $P = 0.45$). Multivariable predictors of LVA were: age ≥ 65 years; serum creatinine ≥ 85 μmol/L on admission; pulse pressure ≤ 45 mmHg on admission; presence of a Q wave on admission electrocardiogram; Thrombolysis In Myocardial Infarction flow grade < 3 after percutaneous coronary intervention; 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 $P = 0.23$).
Conclusions. — 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 the patient's 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.

MOTS CLÉS
Syndrome coronarien aigu avec sus-décalage du segment ST ;
Arythmies ventriculaires ;
Pronostic ;
Score de risque

Résumé
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+).
Méthodes. — Les données de 13 523 patients inclus dans un registre prospectif ont été utilisées. Des régressions logistiques et de Cox ont été utilisées pour identifier les facteurs prédictifs d'AVP, AVT et mortalité hospitalière. Un score de risque d'AVT a été créé à partir des facteurs prédictifs identifiés.

Résultats. — Une AVP est survenue chez 687 patients (5 %) alors que 120 patients (0,9 %) ont présenté une AVT à un délai médian 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 étaient : un age ≥ 65 années ; 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) ; et haut (≥ 45). Les taux d'AVT observés 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).
Conclusions. — Les AVP sont 5 fois plus fréquentes que les AVT en post-SCA ST+ et s'associent à un haut risque 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 risque identifiant les patients à haut risque d'AVT pour lesquels une sortie précoce d'une unité de soins intensifs pourrait ne pas être souhaitable.

Background

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

Mechanisms in the genesis of VA have been well identified, including automaticity, triggered activity and re-entry. Ischaemia and reperfusion induce precipitating factors, ranging from ionic disturbances and 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 VAs into different categories of timing after STEMI and primary PCI, demonstrating that the timing of VA occurrence influences its incidence, risk factors and clinical significance. Overall, the majority of VAs occur early (EVA), within 24—48 hours of symptom onset. However, a sizeable proportion of VAs occur after this cut-off, and a recent study suggests that late VA (LVA) portends a poorer prognosis, with higher in-hospital mortality [6,7]. Specialized units, such as cardiac intensive care units (ICUs) or coronary care units, are the ideal setting for treating VA in an optimal and timely manner. The length of ICU stay has reduced progressively over time as a result of earlier revascularization. Current guidelines recommend that the length of ICU stay and electrocardiogram monitoring should be determined on an individual basis [1]. Thus, it is crucial to identify risk factors for LVA that would help to distinguish patients who may benefit from longer surveillance in the ICU. Nevertheless, there is no formal definition of LVA, and the largest reports have defined it as any VA occurring after cardiac catheterization, which may not be the most clinically relevant cut-off [8—10].

Using a large prospective multicentre registry of patients with STEMI (Observatoire Régional Breton sur l'Infarctus [ORBI]; Brittany Regional Infarction Observatory), 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.

Methods

The ORBI registry

This observational study used data from ORBI, which prospectively includes all patients admitted since 2006 to any of the nine participating interventional cardiology centres located in Brittany, France, for STEMI (final diagnosis), within 24 hours of symptom onset. Demographic data, patient medical background, haemodynamic status, pre- and in-hospital delays before medical care and primary PCI, 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 analysed. Patients with data available on the occurrence and timing of VA were included, and were separated into 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, of ≥ 1 mm in two contiguous leads or as 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 electrocardiogram or cardiac monitoring. EVA was defined as any VA occurring on the day of symptom onset or the next day (day 0 or 1), including before and during primary PCI; LVA was defined as VA occurring between day 2 and discharge. Early complications were defined as occurring on the day of symptom onset or the next day. First medical contact was defined according to the 2008 European Society of Cardiology STEMI guidelines [14]. Total ischaemic time was defined as the time between symptom onset and initiation of reperfusion (balloon inflation or thromboaspiration in the case of primary PCI or administration of fibrinolytic treatment in the case of fibrinolysis); and first medical contact-to-treatment delay was defined as the time between first medical contact and initiation of reperfusion. Mechanical circulatory assistance included an intra-aortic balloon pump, extracorporeal membrane oxygenation and the Impella left ventricular assist device (Abiomed, Danvers, MA, USA). Mechanical complication was defined as the occurrence of either ischaemic mitral regurgitation or ventricular septal rupture. High-degree atrioventricular block was defined as third- or second-degree type 2 atrioventricular block.

Outcomes

The primary outcome was the occurrence and timing of sustained VA as defined previously. Secondary outcomes included in-hospital major adverse cardiac events, 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 were analysed according to timing of occurrence. The impact of VA upon in-hospital mortality was also assessed.

Statistical analysis

Data are summarized as number (percentage) for categorical variables. Continuous variables are expressed as median (interquartile range). Qualitative data were compared using the Chi^2 test or Fisher's exact test, whereas continuous data were compared using the Mann—Whitney U test. All tests were two-sided at the 0.05 significance level. Kaplan—Meier time-to-event curves were used to analyse in-hospital mortality according to VA occurrence and timing. Univariate and multivariable Cox regression was performed to identify independent predictors of in-hospital mortality. Predictors of EVA and LVA were evaluated using univariate and multivariable logistic regression. All univariate 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 one 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 univariate analysis were entered into 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 categorize continuous variables with a univariate P-value < 0.10 by selecting clinically relevant cut-offs, which were the closest to the optimal cut-off, according to 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 versus 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, of whom 13,523 (mean age 62.1 ± 10.0 years; male sex 77%) had data available regarding the occurrence and timing of VA, and were included in this study. Overall, 5.9% of patients ($n = 798$) had VA recorded during their hospital stay; 678 (85%) were classified as having EVA and 120 (15%) were classified as having LVA, the latter presenting VA at a median of 3 days after STEMI. Fig. 1 shows the daily number of patients with LVA according to time from symptom onset. Among patients with EVA, 285 (42.0%) presented sustained ventricular tachycardia compared with 97 (80.8%) among patients with LVA ($P < 0.001$). Conversely, 440 patients with EVA (64.9%) and 37 of their LVA counterparts (30.8%) presented ventricular fibrillation ($P < 0.001$).

Baseline characteristics of patients according to occurrence of VA are presented in Table 1. Compared with patients without VA, patients who developed VA during their hospital stay had signs of poorer haemodynamic status on admission, with a higher rate of Killip class III/IV heart failure, lower blood pressure and a higher creatinine concentration. Patients in the LVA group were significantly older than those in the EVA group. Total ischaemic time was significantly longer in the LVA group compared with the EVA group,

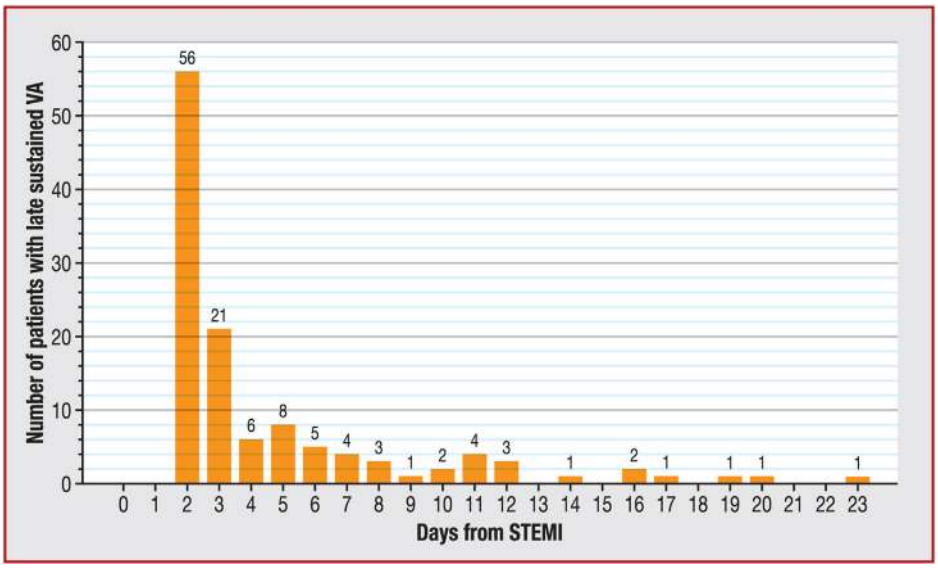

Figure 1. Number of patients who developed late ventricular arrhythmia (VA) according to time after admission for ST-segment elevation myocardial infarction (STEMI).

and the rate of Q wave on the admission electrocardiogram was higher in the LVA group.

There were significant differences in acute phase management between the no VA, EVA and LVA groups (Table 2). Patients who developed VA were more likely to have a left main coronary artery lesion, whether culprit or not, and impaired flow in the culprit artery at the time of primary PCI (Thrombolysis In Myocardial Infarction [TIMI] flow grade 3 before primary PCI: 13.5% for the EVA group and 12.8% for the LVA group versus 24.2% for the no VA group; $P < 0.001$).

Table A.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 guideline-recommended therapies within 48 hours of admission.

In-hospital outcomes

VAs were associated with an increased risk of in-hospital major adverse cardiac events (24.6% for EVA and 23.3% for LVA versus 5.6% for no VA; $P < 0.001$), all-cause mortality (20.2% for EVA and 22.5% for LVA versus 4.1% for no VA; $P < 0.001$) (Fig. 2) and most individual STEMI complications (Table 3). Compared with patients with EVA, those with LVA were associated with higher rates of development of Killip III/IV heart failure (27.0% vs. 15.3%) and mechanical complications (10.0% vs. 3.5%), and with a longer length of stay in the ICU and hospital.

Predictors of EVA

Table 4 summarizes the predictors of EVA. Covariates independently associated with an increased risk of EVA included higher glycaemia on admission, a shorter symptoms-to-first medical contact delay, lower pulse pressure, a depressed LVEF, the presence of Killip class III/IV heart failure on

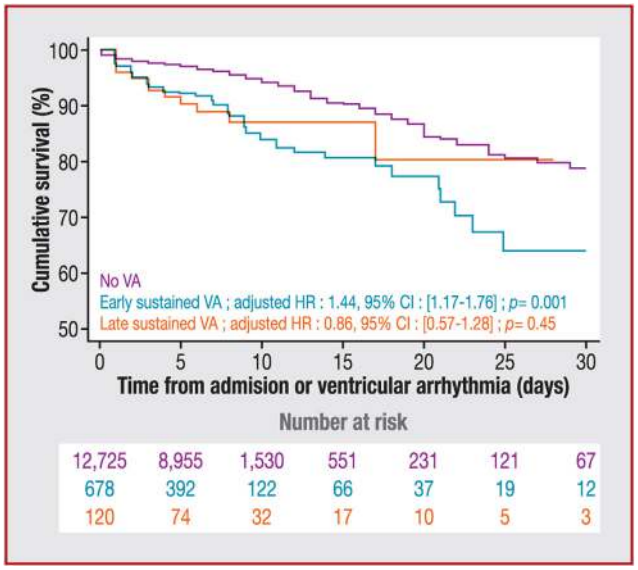

Figure 2. Kaplan–Meier time-to-event curves showing cumulative rates of in-hospital all-cause mortality according to the occurrence and timing of ventricular arrhythmia (VA). Time when subjects become at risk was set as admission for ST-segment elevation myocardial infarction for patients without VA, and as date of VA for other patients. CI: confidence interval; HR: hazard ratio.

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 thrombosis was the strongest predictor of EVA (odds ratio: 4.15, 95% confidence interval [CI]: 2.35–7.33; $P < 0.001$).

Predictors of LVA

Univariate and multivariable predictors of LVA are listed in Table A.2. Seven predictors were independently associated with LVA in the multivariable analysis: age $\geq$ 65 years; serum

Table 1 Baseline characteristics of the study population according to the occurrence and timing of sustained ventricular arrhythmia.

	No sustained VA (*n* = 12,725)	Early sustained VA (*n* = 678)	Late sustained VA (*n* = 120)	*P*
Clinical characteristics				
Age (years)	62.0 (53.0—73.0)	62.0 (52.0—73.0)	72.0 (60.0—81.0)	< 0.001[a,b]
Male sex	9887 (77.7)	512 (75.5)	93 (77.5)	0.41
Body mass index (kg/m^2)	26.0 (24.0—29.0) (*n* = 12,396)	26.0 (24.0—29.0) (*n* = 633)	26.0 (24.0—29.0) (*n* = 115)	0.61
Familial history of coronary artery disease	3188/12,422 (25.7)	147/652 (22.5)	20/115 (17.4)	0.03
Hypertension	5095/12,695 (40.1)	282/674 (41.8)	52/120 (43.3)	0.53
Diabetes mellitus	1282/12,615 (10.2)	58/672 (8.6)	14/119 (11.8)	0.37
Dyslipidaemia	5251/12,357 (42.5)	271/656 (41.3)	54/119 (45.4)	0.68
Current smoker	4910/12,643 (38.8)	274/668 (41.0)	46/119 (38.7)	0.53
Previous myocardial infarction	1025/12,697 (8.1)	63/676 (9.3)	10/120 (8.3)	0.51
Previous CABG	161/12,699 (1.3)	7/676 (1.0)	1/120 (0.8)	0.91
Previous PCI	1187/12,694 (9.4)	64/674 (9.5)	13/120 (10.8)	0.85
Chronic obstructive pulmonary disease	624/1,2689 (4.9)	39/673 (5.8)	11/120 (9.2)	0.07
Previous stroke/TIA	475/12,692 (3.7)	22/673 (3.3)	9/120 (7.5)	0.09
Peripheral artery disease	527/12,689 (4.2)	36/673 (5.3)	10/120 (8.3)	0.03
Permanent pacemaker	83/12,690 (0.7)	5/673 (0.7)	1/120 (0.8)	0.94
Presentation				
Presentation as cardiac arrest	345/12,458 (2.8)	65/665 (9.8)	6/119 (5.0)	< 0.001[c]
Admission to a non-PCI-capable centre	2619 (20.6)	130 (19.2)	23 (19.2)	0.63
Managed by mobile ICU	7644 (60.1)	424 (62.5)	74 (61.7)	0.42
Treatment delays (minutes)				
Symptoms-to-first medical contact delay	97 (55—192) (*n* = 11,655)	75 (40—175) (*n* = 641)	120 (60—210) (*n* = 109)	< 0.001[b,c]
First medical contact-to-treatment delay	93 (72—130) (*n* = 10,764)	95 (73—130) (*n* = 601)	119 (82—153) (*n* = 97)	0.007[a,b]
Symptoms-to-treatment delay	205 (146—321) (*n* = 10,784)	183 (140—270) (*n* = 578)	223 (163—335) (*n* = 95)	< 0.001[b,c]
Electrocardiogram on admission				
Q wave	3724/12,663 (29.4)	201/669 (30.0)	58/119 (48.7)	< 0.001[a,b]
Left bundle branch block	275/12,660 (2.2)	27/675 (4.0)	2/120 (1.7)	0.01[c]
Anterior myocardial infarction	5221 (41.0)	297 (43.8)	56 (46.7)	0.17
Haemodynamics on admission				
Killip class III/IV	579/12,656 (4.6)	135/664 (20.3)	16/118 (13.6)	< 0.001[a,c]
Heart rate (beats/min)	75 (64—87) (*n* = 12,355)	77 (63—90) (*n* = 640)	83 (70—99) (*n* = 115)	< 0.001[a,b]
Systolic blood pressure (mmHg)	133 (117—150) (*n* = 12,460)	120 (100—141) (*n* = 643)	120 (107—140) (*n* = 114)	< 0.001[a,c]
Pulse pressure (mmHg)	51 (40—66) (*n* = 12,431)	44 (33—56) (*n* = 640)	43 (35—56) (*n* = 113)	< 0.001[a,c]
Blood tests on admission				
Serum creatinine concentration (μmol/L)	80 (68—93) (*n* = 12,460)	86 (72—104) (*n* = 651)	91 (73—114) (*n* = 118)	< 0.001[a,c]

Table 1 (*Continued*)

	No sustained VA ($n = 12,725$)	Early sustained VA ($n = 678$)	Late sustained VA ($n = 120$)	*P*
Glomerular filtration rate (MDRD) (mL/min/1.73 m^2)	87 (71—103) ($n = 12,460$)	80 (62—98) ($n = 651$)	73 (54—95) ($n = 118$)	< 0.001[a,c]
Glycaemia (mmol/L)	7.3 (6.2—9.0) ($n = 11,896$)	8.7 (6.9—11.5) ($n = 603$)	8.6 (7.0—11.0) ($n = 112$)	< 0.001[a,c]

Data are expressed as median (interquartile range) or number (%). CABG: coronary artery bypass graft; ICU: intensive care unit; MDRD: calculated using the Modification of Diet in Renal Disease study equation; PCI: percutaneous coronary intervention; TIA: transient ischaemic attack; VA: ventricular arrhythmia.

[a] Denotes a significant Bonferroni-corrected post-hoc pairwise comparison between the ''no sustained VA'' and ''late sustained VA'' groups.

[b] Denotes a significant Bonferroni-corrected post-hoc pairwise comparison between the ''early sustained VA'' and ''late sustained VA'' groups.

[c] Denotes a significant Bonferroni-corrected post-hoc pairwise comparison between the ''no sustained VA'' and ''early sustained VA'' groups.

creatinine ≥ 85 μmol/L (0.97 mg/dL) on admission; pulse pressure ≤ 45 mmHg on admission; presence of a Q wave on admission electrocardiogram; PCI TIMI flow grade < 3 after PCI; and LVEF $\leq 45\%$. 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 for the Hosmer-Lemeshow goodness-of-fit test was 0.23.

LVA risk score building

Points assigned to each variable of the risk scoring system were derived from the regression coefficients of the final multivariable model (Fig. 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 LVA is shown in Fig. A.1. Fig. A.2 illustrates the calibration plot of predicted versus 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 $\leq 0.27\%$ (median 0.15%); low-to-intermediate risk for a score ≥ 23 and ≤ 34, corresponding to a predicted incidence > 0.27% and $\leq 0.58\%$ (median 0.38%); intermediate-to-high risk for a score ≥ 35 and ≤ 44, corresponding to a predicted incidence > 0.58% and $\leq 1.06\%$ (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%, respectively.

Predictors of in-hospital mortality

Univariate 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% CI: 1.17—1.76; $P = 0.001$) whereas LVA *per se* was not a risk factor for in-hospital death (hazard ratio: 0.86, 95% CI: 0.57—1.28; $P = 0.45$) (Fig. 2).

Discussion

To the best of our knowledge, the present study involves the largest cohort of patients with STEMI in the primary PCI era, with a focus on VA incidence, timing and predictors. Among 13,523 patients, VA occurred in 798 patients (5.9%), 120 (0.9%) of whom developed LVA at or beyond day 2 after symptom onset. EVA was approximately 5-fold more common than LVA, and was associated with an increased risk of in-hospital mortality. Predictors of EVA were mainly related to poorer haemodynamic status on admission, larger infarct size and several early STEMI complications or interventions required to treat these complications. Early stent thrombosis was the strongest predictor of EVA. In contrast, LVA was not related to these early complications, but rather was associated with the baseline risk profile of patients (older age, renal function, poorer haemodynamics) and infarct size (Q-wave on admission, TIMI flow grade < 3 after primary PCI, 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 electrocardiogram monitoring period may not be suitable.

LVA 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 patients with STEMI enrolled between 2004 and 2006, LVA was defined as any sustained ventricular tachycardia/fibrillation occurring after cardiac catheterization [9]. 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 3485 patients undergoing primary PCI [10], and by Huang et al. in their recent retrospective study of 607 patients with STEMI [17]. Another study chose to define late VA as occurring more than 1 hour after cardiac

Table 2 Acute phase management of and angiographic findings for the study population according to the occurrence and timing of sustained ventricular arrhythmia.

	No sustained VA (*n* = 12,725)	Early sustained VA (*n* = 678)	Late sustained VA (*n* = 120)	*P*
Acute management strategy				
Primary PCI	10,101 (79.4)	561 (82.7)	100 (83.3)	0.011[a]
Fibrinolysis	1134 (8.9)	70 (10.3)	5 (4.2)	
Secondary PCI	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	12,543 (98.6)	669 (98.7)	118 (98.3)	1.00
Radial access	7907/11,123 (71.1)	332/607 (54.7)	56/108 (51.9)	< 0.001[a,b]
Significant lesions				
Left anterior descending artery	8116/12,446 (65.2)	447/668 (66.9)	82/118 (69.5)	0.42
Left circumflex coronary artery	5036/12,443 (40.5)	261/668 (39.1)	45/118 (38.1)	0.68
Right coronary artery	7233/12,438 (58.2)	395/667 (59.2)	64/118 (54.2)	0.59
Left main coronary artery	445/12,439 (3.6)	43/668 (6.4)	11/118 (9.3)	< 0.001[a,b]
Coronary anatomy	(*n* = 12,308)	(*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	5207/12,448 (41.8)	284/668 (42.5)	56/118 (47.5)	0.44
Left circumflex coronary artery	1961/12,446 (15.8)	96/668 (14.4)	18/118 (15.3)	0.63
Right coronary artery	5187/12,446 (41.7)	274/668 (41.0)	40/118 (33.9)	0.22
Left main coronary artery	101/12,446 (0.8)	19/668 (2.8)	5/118 (4.2)	< 0.001[a,b]
PCI performed	11,477 (90.2)	637 (94.0)	110 (91.7)	0.005[a]
TIMI flow grade 3 before PCI	2996/12,381 (24.2)	90/666 (13.5)	15/117 (12.8)	< 0.001[a,b]
Thromboaspiration	5265/11,475 (45.9)	348/637 (54.6)	61/110 (55.5)	< 0.001[a]
Glycoprotein IIb/IIIa inhibitor use	4984/12,717 (39.2)	314/677 (46.4)	47/120 (39.2)	0.001[a]
Stent implantation	(*n* = 11,411)	(*n* = 632)	(*n* = 106)	0.002[a,b]
No stent	890 (7.8)	74 (11.7)	13 (12.3)	
Bare-metal stent	5609 (49.2)	318 (50.3)	57 (53.8)	
Drug-eluting stent	4912 (43.0)	240 (38.0)	36 (34.0)	
TIMI flow grade 3 after PCI	10,827/11,384 (95.1)	566/630 (89.8)	83/104 (79.8)	< 0.001[a,b,c]
Complete revascularization after index procedure	5422/11,459 (47.3)	289/637 (45.4)	50/110 (45.5)	0.59

Data are expressed as number (%). PCI: percutaneous coronary intervention; TIMI: Thrombolysis In Myocardial Infarction; VA: ventricular arrhythmia.

[a] Denotes a significant Bonferroni-corrected post-hoc pairwise comparison between the ''no sustained VA'' and ''early sustained VA'' groups.

[b] Denotes a significant Bonferroni-corrected post-hoc pairwise comparison between the ''no sustained VA'' and ''late sustained VA'' groups.

[c] Denotes a significant Bonferroni-corrected post-hoc pairwise comparison between the ''early sustained VA'' and ''late sustained VA'' groups.

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

Outcomes	No sustained VA ($n = 12,725$)	Early sustained VA ($n = 678$)	Late sustained VA ($n = 120$)	*P*
Major adverse cardiovascular events	710 (5.6)	167 (24.6)	28 (23.3)	< 0.001[a,b]
All-cause mortality	528 (4.1)	137 (20.2)	27 (22.5)	< 0.00[a,b]
Cardiovascular mortality	487 (3.8)	130 (19.2)	25 (20.8)	< 0.001[a,b]
Non-fatal myocardial infarction	115 (0.9)	23 (3.4)	2 (1.7)	< 0.001[a]
Stent thrombosis	94 (0.7)	23 (3.4)	1 (0.8)	< 0.001[a]
Stroke	62 (0.5)	10 (1.5)	0 (0.0)	0.009[a]
Development of Killip class III/IV heart failure	572 (4.5)	101 (15.3)	31 (27.0)	< 0.001[a,b,c]
Mechanical complications	429 (3.4)	24 (3.5)	12 (10.0)	0.003[b,c]
High-degree atrioventricular block	405 (3.2)	60 (8.8)	10 (8.3)	< 0.001[a,b]
New-onset atrial fibrillation/flutter	498/9593 (5.2)	52/489 (10.6)	17/90 (18.7)	< 0.001[a,b]
Right ventricular myocardial infarction	228 (1.8)	40 (5.9)	9 (7.5)	< 0.001[a,b]
Major bleeding (BARC classification 3 or 5)	191/8423 (2.3)	33/450 (7.3)	9/79 (11.4)	< 0.00[a,b]
ICU length of stay (days)[d]	3.0 (3.0—5.0) ($n = 12,170$)	4.0 (3.0—6.0) ($n = 540$)	6.0 (4.0—11.0) ($n = 92$)	< 0.001[a,b,c]
Total hospitalization length of stay (days)[d]	5.0 (4.0—7.0) ($n = 12,175$)	7.0 (5.0—10.0) ($n = 540$)	11.0 (7.0—17.0) ($n = 93$)	< 0.001[a,b,c]

Data are expressed as number (%) or median (interquartile range). BARC: Bleeding Academic Research Consortium; ICU: intensive care unit; VA: ventricular arrhythmia.

[a] Denotes a significant Bonferroni-corrected post-hoc pairwise comparison between the ''no sustained VA'' and ''early sustained VA'' groups.

[b] Denotes a significant Bonferroni-corrected post-hoc pairwise comparison between the ''no sustained VA'' and ''late sustained VA'' groups.

[c] Denotes a significant Bonferroni-corrected post-hoc pairwise comparison between the ''early sustained VA'' and ''late sustained VA'' groups.

[d] Among patients discharged alive from the hospital.

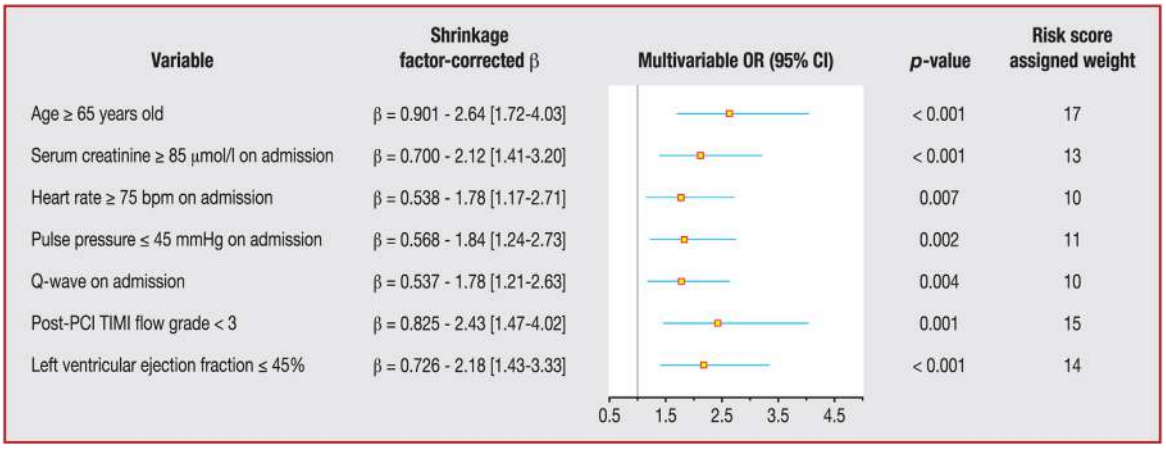

Figure 3. Multivariable predictors of late ventricular arrhythmias and their respective weights in the late ventricular arrhythmia predictive score. b.p.m.: beats per minute; CI: confidence interval; OR: odds ratio; PCI: percutaneous coronary intervention; TIMI: Thrombolysis In Myocardial Infarction.

catheterization [18]. In the present study, the cut-off of day 2 after symptom onset used to define LVA was chosen for its clinical relevance, as identifying patients at higher risk of VA beyond this cut-off can justify a delayed discharge from ICU and prolonged electrocardiogram monitoring. Similar definitions were used by Tran et al. in their evaluation of 25-year trends in incidence and case fatality rates of VA complicating acute myocardial infarction in central Massachusetts [19] and by Takada et al. [7].

VA incidence

Although the incidence of significant VA in patients hospitalized for STEMI has been decreasing in recent decades, akin

Table 4 Predictors of early sustained ventricular arrhythmia.

Variables	Univariate OR (95% CI)	*P*	Multivariable OR (95% CI)	*P*
Familial history of coronary artery disease	0.85 (0.70—1.02)	0.08	—	—
Serum creatinine concentration on admission, per 1 μmol/L increase	1.004 (1.002—1.006)	< 0.001	—	—
Glycaemia on admission, per 1 mmol/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 1 minute 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/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 beat/min increase	1.009 (1.005—1.013)	< 0.001	—	—
Pulse pressure, per 1 mmHg 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 coronary artery	3.44 (2.10—5.64)	< 0.001	—	
TIMI flow grade < 3 after PCI	2.13 (1.63—2.80)	< 0.001	—	
LVEF, 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

CI: confidence interval; LVEF: left ventricular ejection fraction; OR: odds ratio; PCI: percutaneous coronary intervention; TIMI: Thrombolysis In Myocardial Infarction.

to other STEMI complications, as a result of improvements in the performance and timeliness of reperfusion therapies, VA remains a common and possibly life-threatening complication [8]. 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 of ventricular fibrillation from 8.2% to 1.7% [19]. The definition of ventricular tachycardia as any cardiac arrhythmia of at least three consecutive complexes originating in the ventricles at a rate of greater than 100 beats/min used in this study probably explains the higher incidence rates observed compared with other recent studies. The 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 centres in 17 countries [9]; it also showed that the incidence of VA differs depending on the timing in relation to reperfusion: prereperfusion VA was more frequent than reperfusion-induced VA or VA occurring early or late after reperfusion [9]. Similarly, in our study, the occurrence of LVA decreased exponentially with time from symptom onset, with a median delay of 3 days (Fig. 1).

Predictors of VA

Previous studies have sought to determine predictors of VA in patients hospitalized for STEMI, although with smaller cohorts [8,9,17,18]. Some predictors were similar to those found in the present study, particularly surrogate markers of larger infarct size or heart failure, such as low systolic blood pressure, higher heart rate or lower LVEF. In a substudy based on the HORIZONS-AMI trial population, Mehta et al. found that the stronger predictors of VA were Killip class > I and a thrombotic culprit lesion at baseline [10]. Unlike previous studies, patients' cardiovascular risk factors were not predictive of VA in the present study. However, although its relationship with the risk of VA after STEMI is complex, involving elevated sympathetic activity and acute inflammatory processes [20], 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 with other territories [9]. 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 [8]. 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 with LVA, EVA was more likely to present as ventricular fibrillation (64.9% vs. 30.8%), whereas LVA presented more often 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

Table 5 Predictors of in-hospital mortality.

Variables	Univariate HR (95% CI)	*P*	Multivariable HR (95% CI)	*P*
Sustained VA				
Early sustained VA	3.93 (3.25—4.77)	< 0.001	1.44 (1.17—1.76)	0.001
Late sustained VA	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 CABG	2.18 (1.40—3.41)	0.001	—	—
Chronic obstructive pulmonary disease	1.50 (1.14—1.97)	0.004	—	—
Previous stroke/TIA	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 concentration on admission, per 1 μmol/L increase	1.006 (1.005—1.006)	< 0.001	1.004 (1.003—1.005)	< 0.001
Glycaemia on admission, per 1 mmol/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 centre	0.77 (0.63—0.95)	0.014	0.80 (0.64—0.99)	0.04
Managed by mobile ICU	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/IV heart failure	22.12 (18.43—26.56)	< 0.001	4.49 (3.59—5.61)	< 0.001
Heart rate, per 1 beat/min increase	1.02 (1.01—1.02)	< 0.001	—	—
Systolic blood pressure, per 1 mmHg increase	0.97 (0.97—0.97)	< 0.001	0.993 (0.990—0.995)	< 0.001
Acute management strategy				
Primary PCI	Ref.			
Fibrinolysis	1.13 (0.86—1.48)	0.38	1.79 (1.34—2.39)	< 0.001
Secondary PCI	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
LVEF, per 1% increase	0.91 (0.90—0.92)	< 0.001	0.966 (0.960—0.973)	< 0.001
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	—	—

CABG: coronary artery bypass graft; CI: confidence interval; HR: hazard ratio; ICU: intensive care unit; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention; TIA: transient ischaemic attack; VA: ventricular arrythmia.

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 an optimized antithrombotic 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 was associated with 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% in patients without VA [6]. Similarly, VA was associated with a more than 3-fold

higher 90-day mortality after adjustment for confounders in the APEX-AMI substudy [9]. In contrast, VA did not influence in-hospital and 1-year mortality in the PAMI substudy [8]. Interestingly, LVA was 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 for this finding could be the fact that patients admitted for STEMI were seldom discharged from the ICU within 48 hours of symptom onset in centres 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 centres routinely performing early discharge from the 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.

Study 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 centre, which may induce selection bias; STEMI cases managed medically in non-interventional centres or patients who do not survive the prehospital phase are not enrolled. Another limitation of this study is the absence of certain biological variables of importance in VA incidence, such as blood potassium concentrations, 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.

Conclusions

In a contemporary cohort of patients with STEMI, VA was a common complication, affecting approximately 5% of patients. Early VA portends an increased risk of in-hospital mortality. VA occurrence diminishes with time from STEMI, but a significant number of VAs (15% of all VAs) occur at or beyond 2 days of symptom onset. The risk score derived in this study can help to 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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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.acvd.2021.10.012.

Disclosure of interest

The authors declare that they have no competing interest.

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