


Factors that predict ventricular arrhythmias in the late phase after acute myocardial infarction

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Abstract

Aims Little is known regarding factors that predict the occurrence of lethal ventricular arrhythmias (VAs) occurring after acute myocardial infarction (AMI). This observational cohort study aimed to identify factors that predicted lethal VAs during the late phase after AMI in patients with reduced left ventricular ejection fraction (LVEF).

Methods and results Data were collected from our AMI database regarding consecutive patients with an LVEF of $\leq 40\%$ after AMI (January 2012 to July 2018). The 'late phase' was defined as ≥ 7 days after AMI onset, and the primary endpoint was defined as lethal VAs in the late phase. The study included 136 patients (82% men; mean age: 66 ± 13 years). The average LVEF at admission was $32.7 \pm 8.2\%$. During a mean follow-up period of 20.7 months, 14 patients (10%) experienced lethal VAs, including ventricular fibrillation ($n = 8$) and sustained ventricular tachycardia ($n = 10$). Univariate analyses revealed that lethal VAs were predicted by age and LVEF at admission. Receiver operating characteristic curve analysis indicated that the optimal cut-off value was 23% for using the LVEF at admission to predict the primary endpoint (area under the curve: 0.77, $P < 0.0001$). Multivariable analysis also demonstrated that LVEF at admission was an independent predictor of the primary endpoint (risk ratio = 7.12, $P = 0.001$).

Conclusions Lethal VAs in the late phase are common in patients with AMI, and reduced LVEF and cardiac function at admission play a significant role in the risk stratification for future lethal VAs in this population.

Keywords Myocardial infarction; Reduced left ventricular ejection fraction; Ventricular arrhythmia

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Introduction

Acute myocardial infarction (AMI) causes severe left ventricular (LV) dysfunction that can persist even after successful reperfusion therapy. This phenomenon is associated with increased mortality from both congestive heart failure and sudden cardiac death caused by lethal ventricular arrhythmias (VAs), such as ventricular fibrillation and sustained ventricular tachycardia.^{1–4}

Primary percutaneous coronary intervention (PCI) is currently performed as reperfusion therapy and has contributed to decreased mortality after AMI. Optimal medical therapy, such as antiplatelet drugs, beta-blockers, statins, and angiotensin-converting enzyme inhibitors, has also improved the

prognosis of these patients.^{5–8} However, in the 'primary PCI era', the mortality rate remains high among patients with LV dysfunction after AMI.⁹ Patients with a left ventricular ejection fraction (LVEF) of $\leq 40\%$ after AMI have an increased risk of sudden cardiac death and mortality.^{10–12} Non-sustained ventricular tachyarrhythmia, which is often documented in the acute phase after AMI, is also a reported risk factor for ventricular tachycardia or ventricular fibrillation in patients with reduced LVEF.^{13,14} However, little is known regarding which patients with heart failure after AMI should be considered for prophylactic therapies, such as an implantable cardioverter-defibrillator. This study aimed to investigate the prognostic factors and significance of VAs in the late phase among patients with reduced LVEF after AMI. We

hypothesized that LVEF at admission would be an independent predictor of lethal VAs in the late phase after AMI.

Methods

This single-centre retrospective observational study evaluated 628 patients who underwent urgent coronary angiography due to AMI between January 2012 and July 2018 at Chiba University Hospital, Japan. Written informed consent for the examination was obtained from all patients. The retrospective study protocol was approved by the ethical committee of Chiba University and conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Patients were considered eligible for this study if they received any form of reperfusion therapy and their LVEF at admission was $\leq 40\%$. The presence of AMI was defined in accordance with the third universal definition of myocardial infarction.¹⁵ The major exclusion criteria were multiple admissions, myocardial damage caused by other reasons that did not require any reperfusion therapy (e.g. Takotsubo syndrome, vasospastic angina, and myocarditis), death during the initial hospitalization, lack of reperfusion therapy, and post-resuscitation encephalopathy.

After admission, coronary angiography was performed for all patients, and the operator selected the optimal therapy (PCI, coronary bypass graft, or conservative therapy) based on the results. When PCI was considered suitable, patients were administered aspirin (200 mg) and clopidogrel (300 mg) or prasugrel (20 mg) before the procedure.⁸ The PCI was performed under local anaesthesia, and intravenous heparin was administered during the procedure to maintain the activated clotting time at 250–400 s. The decision to use a drug-eluting stent, a bare-metal stent, or a drug-coated balloon was at the operator's discretion, and other procedural approaches, including the use of intravascular ultrasound imaging, were based on current standardized care.^{16–18} Follow-up was planned as outpatient clinic visits or via telephone consultation, as needed.

Baseline data for all patients were collected from electronic health records available at our hospital. We defined the 'acute phase' as < 48 h after AMI, the 'sub-acute phase' as 48 h to 7 days after AMI, and the 'late phase' as > 7 days after AMI. The primary endpoint was defined as lethal VAs in the late phase after AMI, which included ventricular fibrillation and sustained ventricular tachycardia. The secondary endpoint was any major adverse cardiac event, which was defined as a composite of all-cause death, AMI, target vessel revascularization, and hospitalization for heart failure. Information regarding these events was collected from medical records and implantable cardioverter-defibrillator records.

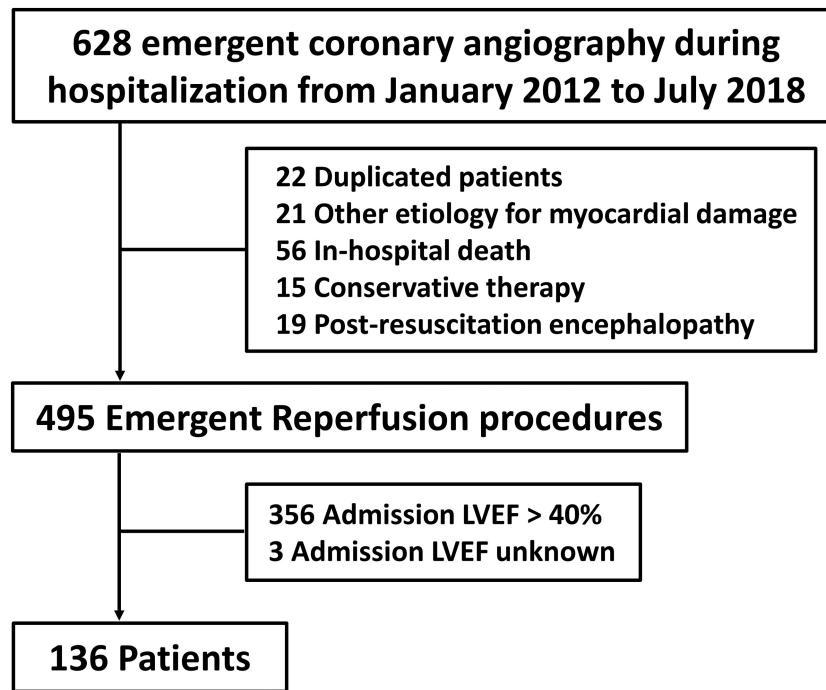
Statistical analysis was performed using JMP® software (version 13; SAS Institute Inc., Cary, NC, USA). Data are

expressed as mean \pm standard deviation (SD), median (interquartile range), or number (%), as appropriate. The normality of continuous variable distribution was determined using the Shapiro–Wilk test or Kolmogorov–Smirnov test, as appropriate. Differences between baseline characteristics were assessed using Student's *t*-test or Wilcoxon's rank sum test for continuous variables and Fisher's exact test or Pearson's χ^2 test for categorical variables. Univariable analyses were performed using linear regression analysis of rank-transformed outcomes. Variables with *P*-values < 0.05 in the univariable analyses were included in the multivariable analyses, which were performed using multiple linear regression analysis of rank-transformed outcomes. Receiver operating characteristic (ROC) curve analyses were conducted based on the occurrence of the cardiovascular endpoints, and the optimal cut-off value was defined based on the maximum average sensitivity and specificity. Kaplan–Meier analysis with the log-rank test was used to compare event-free survival rates. A Cox proportional hazards model was used to estimate unadjusted and adjusted risk ratios with corresponding 95% confidence intervals (CI). *P*-values < 0.05 were considered statistically significant.

Results

A total of 628 patients underwent urgent coronary angiography at our hospital during the study period. However, we excluded 22 patients who were readmitted, 21 patients with other aetiologies for myocardial damage, 15 patients who underwent conservative management, 19 patients who developed post-resuscitation encephalopathy, and 56 patients who died in the hospital. The remaining 495 patients received some form of reperfusion therapy, although 356 patients had a well-preserved or mid-range LVEF ($> 40\%$) and three patients had an unknown LVEF at admission. Thus, the study ultimately included 136 patients (82% men, mean age: 66 ± 13 years). The study flowchart is shown in *Figure 1*. The mean LVEF at admission was $32.7 \pm 8.2\%$. The patients' baseline characteristics are shown in *Table 1*.

Among the included patients, 107 (79%) had ST-segment elevation myocardial infarction and 29 (21%) had non-ST-elevation myocardial infarction. Single-vessel coronary artery disease was observed in 125 patients (92%) and multi-vessel disease in 11 patients (8%). The major culprit vessels were the left main trunk or left anterior descending artery (68%), right coronary artery (25%), and left circumflex coronary artery (18%). Two patients (1%) underwent urgent or semi-urgent coronary artery bypass graft (CABG), and the other patients (99%) underwent primary PCI, with drug-eluting stents used in 118 patients (87%). After the reperfusion procedures, the median creatine phosphokinase concentration was 2391 (31, 25 687) U/L and the median

Figure 1 Study flowchart. LVEF, left ventricular ejection fraction.

creatinase MB concentration was 221 (2, 1662) ng/mL (*Table 1*). During the initial hospitalization, mechanical rupture occurred in only one patient who had ventricular septal perforation.

Most patients were discharged and received post-MI guideline-directed medical therapy,¹⁹ which included antiplatelet agents (134 patients, 99%), beta-blockers (116 patients, 85%), angiotensin converting enzyme inhibitors (112 patients, 82%), or angiotensin receptor blockers (ARBs; 122 patients, 90%) (*Table 1*). During a mean follow-up period of 20.7 months, 14 patients (10%) experienced lethal VAs, which included ventricular fibrillation ($n = 8$) and sustained ventricular tachycardia ($n = 10$). Of these 14 patients, some experienced multiple events and the details of each event and additional information of each patient with VAs are shown in Supporting Information, *Tables S1–S3*. The secondary endpoint was observed in 40 patients (29%), which included 16 all-cause deaths, 5 AMIs, 11 target vessel revascularizations, and 11 hospitalizations for heart failure.

As shown in *Table 1*, the baseline characteristics of the patients who experienced lethal VAs were different from those of their counterparts in several areas. A Cox proportional hazards regression analysis showed that age, LVEF at admission, and peak creatine phosphokinase concentration were predictors of lethal VAs in the univariable analyses (*Table 2*). Patients who experienced lethal VAs were older, had significantly worse left ventricular dysfunction at admission, and had higher peak creatine phosphokinase and creatinase MB concentrations.

Among these factors, a significant difference in the primary endpoint was observed according to LVEF at admission ($P < 0.0001$). ROC curve analysis revealed that the primary endpoint was best predicted using 23% as the cut-off value for the LVEF at admission (*Figure 2*). Kaplan–Meier analysis revealed a significantly higher incidence of the primary endpoint among patients with an LVEF of $<23\%$ at admission (*Figure 3*). As shown in *Figure 3*, the majority of VAs occurred in the first month after AMI. When patients were divided into two groups according to the LVEF at admission, occurrence of late phase VAs was significantly higher in patients with LVEF at admission $<23\%$ compared with their counterpart ($P < 0.0001$). According to these results, patients with LVEF at admission $<23\%$ could have a certain benefit of wearable cardioverter-defibrillator after AMI. Multivariable analysis also revealed that the LVEF at admission independently predicted the primary endpoint (*Table 2*). However, the primary endpoint was not significantly predicted by any major adverse cardiac events (*Table 3*).

Discussion

The present study demonstrated that patients with reduced LVEF after AMI achieved a poorer prognosis, even in the primary PCI era, with 10% and 29% of these patients experiencing lethal VAs and major adverse cardiac events, respectively. In addition, LVEF at admission was an independent predictor

Table 1 Baseline patient characteristics

	All (n = 136)	VAs (n = 14)	Non-VAs (n = 122)	P-value
Age (years)	66.0 ± 13.1	58.8 ± 13.0	66.8 ± 12.9	0.029
Male sex	111 (82%)	13 (93%)	98 (80%)	0.25
Body mass index (kg/m ²)	24.0 ± 3.7	24.6 ± 2.3	23.9 ± 3.8	0.51
Hypertension	93 (68%)	7 (50%)	86 (71%)	0.11
Diabetes mellitus	55 (40%)	8 (57%)	47 (39%)	0.19
Dyslipidaemia	77 (57%)	8 (57%)	69 (57%)	0.99
Current smoker	51 (38%)	5 (36%)	46 (38%)	0.87
Prior MI	12 (9%)	2 (14%)	10 (8%)	0.45
Serum creatinine (mg/dL)	0.97 (0.43, 10.26)	1.10 (0.68, 5.43)	0.97 (0.43, 10.26)	0.88
BNP (pg/mL)	164 (4, 6895)	513 (15, 3190)	155 (4, 6895)	0.10
Admission LVEF (%)	32.7 ± 8.2	23.9 ± 11.2	33.8 ± 7.2	<0.0001
STEMI	107 (79%)	12 (86%)	95 (78%)	0.50
Reperfusion procedures				
CABG	2 (1%)	1 (7%)	1 (1%)	0.06
Successful PCI	134 (99%)	13 (93%)	121 (99%)	0.63
PCI procedure				
Stent type				
DES	118 (87%)	10 (71%)	108 (89%)	0.07
POBA/DCB/aspiration only	1 (1%)	0 (0%)	1 (1%)	0.73
Total stent number	1.57 ± 0.94	1.21 ± 0.56	1.61 ± 0.97	0.13
IVUS guide	136 (100%)	14 (100%)	122 (100%)	1.00
No/slow flow during PCI	31 (23%)	3 (27%)	28 (24%)	0.83
Culprit vessel				
LMT or LAD	92 (68%)	12 (86%)	80 (66%)	0.13
RCA	32 (25%)	1 (7%)	31 (25%)	0.13
LCX	25 (18%)	1 (7%)	24 (20%)	0.25
Peak CPK (U/L)	2391 (31, 25 687)	114 (3026, 25 687)	2391 (31, 15 769)	0.006
Peak CK-MB (ng/mL)	221 (2, 1662)	331 (4, 1548)	221 (2, 1662)	0.01
Medical treatment at discharge				
Antiplatelet	134 (99%)	14 (100%)	120 (98%)	0.63
Anticoagulant	21 (15%)	5 (36%)	16 (13%)	0.03
Statin	122 (90%)	12 (86%)	110 (90%)	0.60
ACE-I or ARB	112 (82%)	8 (57%)	104 (85%)	0.009
Beta-blocker	116 (85%)	10 (71%)	106 (87%)	0.12
Calcium channel blocker	19 (14%)	1 (7%)	18 (15%)	0.43
Diuretics	68 (50%)	9 (64%)	59 (48%)	0.26
MRA	41 (30%)	10 (71%)	32 (26%)	0.0005
Class III anti-arrhythmic drug	20 (15%)	8 (57%)	11 (9%)	<0.0001
Timing of ICD implantation				
Before AMI	1 (0.7%)	1 (7%)	0 (0%)	
Acute phase after AMI	0 (0%)	0 (0%)	0 (0%)	
Subacute phase after AMI	0 (0%)	0 (0%)	0 (0%)	
Late phase after AMI	13 (10%)	5 (36%)	8 (7%)	

ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMS, bare metal stent; BNP, brain natriuretic peptide; CABG, coronary artery bypass graft; CK-MB, creatine kinase MB; CPK, creatine phosphokinase; DCB, drug-coated balloon; DES, drug-eluting stent; IVUS, intravascular ultrasound; LAD, left anterior descending artery; LCX, left circumflex coronary artery; LMT, left main trunk; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineral corticoid receptor antagonist; PCI, percutaneous coronary intervention; POBA, plain old balloon atherectomy; RCA, right coronary artery; STEMI, ST-elevation myocardial infarction.

of lethal VAs in the late phase after AMI. However, there was no significant relationship between lethal VAs in the late phase after AMI and major adverse cardiac events.

Previous studies have indicated that the risk of sudden cardiac death is higher in patients with reduced LVEF, heart failure, or both factors after AMI.^{20–23} An LVEF of ≤40% was recently described as a cut-off point for risk stratification of sudden cardiac death in this population.^{10,11} In a Japanese study with an average follow-up period of 4.1 years, the mortality rate was 13.1% and the sudden cardiac death rate was 1.2% after AMI.¹² The mean baseline LVEF in that study was 52.5%, and relative to an LVEF of >40%, an LVEF of ≤30% predicted increased risk of sudden cardiac death (hazard ratio [HR]: 5.99, 95% CI: 2.73–3.14, *P* < 0.001) and

mortality (HR: 3.85, 95% CI: 2.96–5.00, *P* < 0.001). Furthermore, an LVEF of 30–40% also predicted increased risk of sudden cardiac death (HR: 3.37, 95% CI: 1.74–6.50, *P* < 0.001) and mortality (HR: 2.06, 95% CI: 1.66–2.57, *P* < 0.001).

In the primary PCI era, the prognosis of patients with AMI and preserved LVEF may be improved. However, the total mortality rate in our study was 12.0% during 19.8 months of follow-up, and the main cause of death was non-cardiac causes among patients with reduced LVEF (≤40%). In addition, at least three of 16 patients (19%) died because of cardiovascular problems and two patients (13%) experienced sudden cardiac death. Thus, the mortality and sudden cardiac death rates in our study were higher than those reported in previous studies.^{12,24,25} This may be related to our focus on

Table 2 Cox proportional hazards analysis of factors that predicted lethal VAs

Variable	Univariable		Multivariable	
	RR	P-value	RR	P-value
Age (years)	0.96	0.05	0.97	0.31
Male sex	2.72	0.27		
BMI	1.05	0.50		
Hypertension	0.44	0.13		
Dyslipidaemia	0.97	0.96		
Diabetes mellitus	2.11	0.17		
Prior MI	1.85	0.45		
Current smoker	0.82	0.72		
VAs at <48 h	0.81	0.71		
VAs at 48 h–7 days	4.56	0.01	1.67	0.43
Serum creatinine (mg/dL)	1.01	0.93		
BNP (pg/mL)	1.00	0.17		
Admission LVEF of <23%	9.67	<0.0001	7.12	0.001
Peak CPK (U/L)	1.00	0.03	1.00	0.44

BMI, body mass index; BNP, brain natriuretic peptide; CPK, creatine phosphokinase; LVEF, left ventricular ejection fraction; MI, myocardial infarction; RR, risk ratio; VAs, ventricular tachyarrhythmias.

high-risk patients with LVEF $\leq 40\%$, who were expected to have poorer clinical outcomes. We used ROC curve analysis to identify an LVEF of $\leq 23\%$ as the optimal cut-off point for predicting the risk of lethal VAs after AMI. Another possible explanation for these results could be the use of advanced medical therapy for secondary MI prophylaxis, as large proportions of patients received antiplatelet agents (134 patients, 99%), beta-blockers (116 patients, 85%), angiotensin converting enzyme inhibitors or ARBs (112 patients, 82%), and statins (122 patients, 90%). In this context, prophylactic medical therapy plays an important role in preventing

ventricular remodelling and cardiovascular events, such as ischaemia, reinfarction, and sudden cardiac death. Thus, a stricter regimen of medical treatments is required to improve the long-term prognosis of these high-risk patients.

The present study revealed that the LVEF at admission independently predicted lethal VAs in the late phase after AMI. However, major adverse cardiac events were not significantly related to lethal VAs in the late phase after AMI. The J-MINUET study recently showed that in-hospital ventricular tachycardia or ventricular fibrillation after AMI were predicted by higher creatine kinase concentrations, Killip class III–IV, initial thrombolysis in myocardial infarction flow grade 0–1, and concomitant chronic kidney disease.¹³ However, we did not have access to data regarding Killip classification or initial thrombolysis in myocardial infarction flow grade, although the univariate analyses revealed that sustained ventricular tachycardia or ventricular fibrillation in the late phase after AMI were predicted by peak creatine phosphokinase concentration and the presence of non-sustained ventricular tachyarrhythmia in the sub-acute phase after AMI. These results are consistent with previously reported results,^{26,27} although the relationships were not significant in our multivariable analysis. In general, the peak creatine phosphokinase concentration and the occurrence of non-sustained ventricular tachyarrhythmia reflect the size of the infarcted area and electrophysiological instability. Thus, it is reasonable that the peak creatine phosphokinase concentration or the occurrence of non-sustained ventricular tachyarrhythmia in the sub-acute phase would not be causally related to VAs in the late phase.

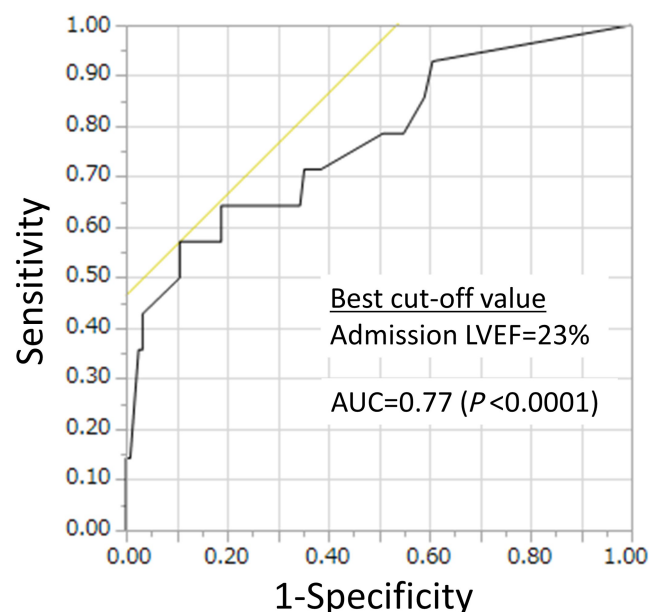
Figure 2 Receiver operating characteristic curve for predicting the primary endpoint revealed that the optimal cut-off value for LVEF at admission was 23%. AUC, area under the curve; LVEF, left ventricular ejection fraction.

Figure 3 Comparison of the cumulative event-free probability between patients with an LVEF of $\geq 23\%$ or $< 23\%$ at admission. Kaplan–Meier analysis revealed a significantly higher incidence of the primary endpoint among patients with an LVEF of $< 23\%$ at admission. LVEF, left ventricular ejection fraction.

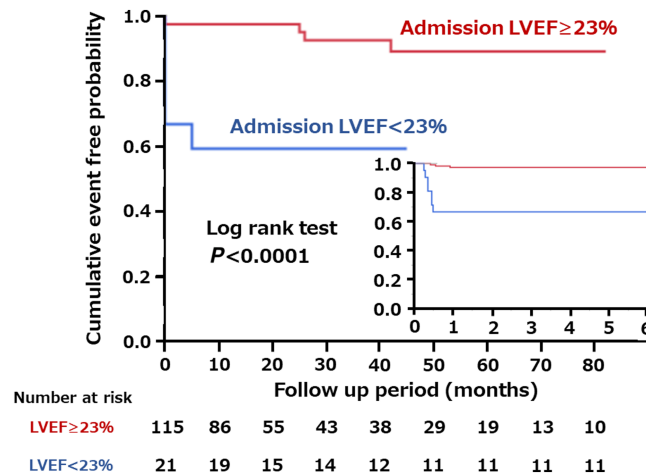


Table 3 Major adverse cardiac events

	VAs (n = 14)	Non-VAs (n = 122)	P-value
MACE	5 (36%)	35 (27%)	0.30
All cause death	2 (14%)	14 (11%)	0.76
Acute myocardial infarction	1 (7%)	4 (3%)	0.47
Target vessel revascularization	2 (14%)	10 (8%)	0.89
Heart failure hospitalization	1 (7%)	10 (8%)	0.89

MACE, major adverse cardiac events; VAs, ventricular tachyarrhythmias.

The presence of non-sustained ventricular tachyarrhythmia in the late phase after AMI is reportedly associated with a poorer prognosis, although its prognostic relevance in the sub-acute phase after AMI remains unclear.²⁸ In the acute and sub-acute phases after AMI, reperfusion arrhythmias occur because of free radicals that are produced when the myocardium is hypo-perfused, and the severity of ischaemia is associated with the prevalence of reperfusion arrhythmia.^{13,29}

The main mechanism of VAs is thought to be abnormal automaticity within 2 weeks after AMI. During this period, the damaged myocardium is replaced by a fibrotic scar that could be the source of abnormal automaticity. Fibrosis of the infarcted myocardium becomes fixed and stabilizes within 2 weeks after AMI, and the myocardium is thought to be in an unstable electrophysiological state during this period.³⁰ The main mechanism responsible for sudden cardiac death in the late phase after MI is thought to be scar-related re-entry, which induces VAs.³¹

Implantable cardioverter-defibrillator therapy currently represents the cornerstone of cardiology practice for

reducing the incidence of sudden cardiac death after MI.^{32,33} However, previous randomized trials did not confirm that early cardioverter-defibrillator implantation reduced the mortality rates among post-MI patients.^{34,35} Thus, in patients with LV dysfunction and AMI, the current guidelines recommend cardioverter-defibrillator implantation only after a period of ≥ 40 days or ≥ 3 months, depending on whether the patient has undergone revascularization.^{32,33} We should carefully consider the ability of such high-risk patients to adapt to the implantable cardioverter-defibrillator after the recommended waiting period. Furthermore, a proportion of post-MI patients eventually recover LV function without further risk of sudden cardiac death (i.e. crossing the LVEF threshold of 35–40%).^{36,37} Thus, the indication for cardioverter-defibrillator implantation should be reassessed using echocardiography (LVEF of $\leq 40\%$ or $> 40\%$) and using 24-h Holter electrocardiography or an event recorder to identify VAs. The results of electrophysiological testing can also be used to assess the prognosis of patients after MI, reduced LVEF, and unsustained VAs.¹⁴

A recent report has indicated that, for patients with a recent MI and reduced LVEF, a wearable cardioverter-defibrillator provided a non-significant lower rate of arrhythmic death (relative risk: 0.67, vs. patients who did not wear the device).³⁶ However, despite enrolling 2302 patients (a large sample for a medical device trial), that study may not have been sufficiently powered to detect a beneficial effect. In addition, low adherence to wearing the device may have limited the potential benefits of the wearable cardioverter-defibrillator. According to the present study, indication of wearable cardioverter-defibrillator should be strengthened, especially in patients with EF lower than 23% after AMI.

This study has some limitations. This was a single-centre study and the number of patients was relatively small. This was a retrospective observational study and patient information was collected from medical records, which raises the possibility that clinical outcomes were not documented precisely. The prevalence of non-sustained ventricular tachyarrhythmia might have been underestimated in the present study, as medical records were used to find patients with this complication and very few patients underwent 24-h Holter electrocardiography. In the present study, the LVEF at admission was obtained before or after reperfusion therapy and the timing of measurement was not defined. Thus, we could not exclude the possibility that LVEF could be affected by myocardial stunning or hibernation in part. In addition, even though ROC analysis for the prediction of VAs lead to the best LVEF cut-off value of 23%, this finding was derived from a very unbalanced group size. Therefore, caution is warranted in extrapolating the present study results in general populations, and further study are needed to confirm this result. Data were not available regarding the time from MI onset to reperfusion therapy and the final thrombolysis in myocardial Infarction grade, which might have influenced the prevalence of VAs.

In conclusion, lethal VAs during the late phase are common in patients with AMI and reduced LVEF. Cardiac function at admission, based on the LVEF, plays a significant role in the risk stratification for future lethal VAs in this population.

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Conflict of interest

None declared.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Clinical data relative to individual events.

Table S2. Clinical data of individual VA events.

Table S3. Patients characteristics.

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