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The significance of early-onset malignant arrhythmias in ST-elevation myocardial infarction patients treated with primary percutaneous coronary intervention and their relationship with biomarkers

Značaj ranih malignih aritmija kod bolesnika sa infarktom miokarda sa ST elevacijom lečenih primarnom perkutanom koronarnom intervencijom i njihova povezanost sa biomarkerima

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Abstract

Background/Aim. Patients who were treated with primary percutaneous coronary intervention (pPCI) and survived ventricular tachycardia (VT) and ventricular fibrillation (VF) in the first 48 hrs after ST-elevation myocardial infarction (STEMI) had, in most investigations, a similar long-term prognosis of the outcome, compared to those patients who did not have VT and VF during the first 48 hrs after STEMI. The aim of the study was to determine the association of myocardial infarction markers: creatine kinase-MB fraction (CK-MB), heart failure marker – B-type natriuretic peptide (BNP), and systemic inflammation factor – C-reactive protein (CRP) with early VT and VF onset, in relation to patient mortality during the first six months after STEMI. **Methods.** The retrospective study included 971 patients with STEMI treated with pPCI for ten years. VF and sustained VT (sVT) were detected outside of the hospital and during the first 48 hrs of hospitalization. **Results.** During the first 48 hrs from admission, 108 (11.1%) patients had life-threatening arrhythmias, of which 75 (69.4%) had VF, and 33 (30.6%) had sVT and were treated with direct current – DC shock and intravenous amiodarone. Intrahospital mortality was significantly higher in patients with VF/sVT in the first 48 hrs compared to patients without VF/sVT (14.8% vs. 5.7%, $p = 0.001$). BNP level had higher accuracy in the prediction of six-month death than the maximum blood level of CRP in patients without VF/sVT after 48 hrs. However, in patients with early-onset malignant arrhythmias, BNP showed a lower level of accuracy in predicting the six-month mortality, as did the CRP values, which had almost the same level of accuracy. Admission glycemia had a much lower predictive value in both groups of patients compared to BNP and CRP [0.705 (0.628–0.781), $p < 0.001$ and 0.662 (0.521–0.803), $p = 0.046$, respectively]. In either of the groups, maximum CK-MB levels were not significant in predicting the six-month all-cause mortality. **Conclusion.** Our study indicates that STEMI patients with early onset of VF and sVT, treated with pPCI, with a high BNP level, have a statistically significantly higher mortality rate compared to patients with a lower BNP level.

Key words:
biomarkers; mortality; percutaneous coronary intervention; prognosis; st elevation myocardial infarction; tachycardia, ventricular; ventricular fibrillation.

Apstrakt

Uvod/Cilj. Bolesnici koji su lečeni primarnom perkutanom koronarnom intervencijom (pPKI) posle infarkta miokarda sa ST elevacijom (*ST-elevation myocardial infarction* – STEMI) i koji su preživeli ventrikularnu tahikardiju (VT) i ventrikularnu fibrilaciju (VF) u prvih 48 sati imali su, u većini istraživanja, sličnu dugoročnu prognozu ishoda u poređenju sa bolesnicima koji nisu imali VT i VF tokom prvih 48 sati nakon STEMI. Cilj rada bio je da se kod bolesnika sa STEMI utvrdi povezanost markera infarkta miokarda: MB frakcije kreatin kinaze (*creatine kinase-MB fraction* – CK-MB), markera srčane insuficijencije – natriuretičkog peptida tipa B (*B-type natriuretic peptide* – BNP) i sistemskog inflamacijskog faktora – C-reaktivnog proteina (CRP) sa ranim početkom VT i VF, u odnosu na mortalitet

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bolesnika tokom prvih šest meseci nakon STEMI. **Metode**. Ovom retrospektivnom studijom obuhvaćeno je 971 bolesnika sa STEMI, lečenih primenom pPKI tokom deset godina. VF i trajna VT (tVT) su detektovane i van bolnice i tokom prvih 48 sati hospitalizacije. **Rezultati.** Tokom prvih 48 sati od prijema, 108 (11,1%) bolesnika imalo je aritmiju opasnu po život, od kojih je 75 (69,4%) imalo VF, a 33 (30,6%) tVT, a lečeni su *direct current* – DC šokom i amjodaronom intravenski. Intrahospitalni mortalitet bio je značajno viši kod bolesnika sa VF/tVT u prvih 48 sati u poređenju sa bolesnicima bez VF/tVT (14,8% vs. 5,7%, $p = 0{,}001$). Nivo BNP pokazao je veću tačnost u predviđanju šestomesečnog mortaliteta u odnosu na vrednost maksimalnog nivoa CRP u krvi kod bolesnika bez VF/tVT nakon 48 sati. Međutim, kod bolesnika sa ranim početkom malignih aritmija, BNP je pokazao niži nivo tačnosti u predviđanju šestomesečnog mortaliteta, kao i vrednosti CRP, koje su imale skoro isti nivo tačnosti. Glikemija na prijemu je imala mnogo nižu prognostičku vrednost u obe grupe bolesnika u poređenju sa BNP i CRP [0,705 (0,628–0,781), $p < 0{,}001$ i 0,662 (0,521–0,803), $p = 0{,}046$, redom]. Ni u jednoj grupi, maksimalni nivoi CK-MB nisu imali značaj u predviđanju šestomesečnog mortaliteta izazvanog bilo kojim od uzroka. **Zaključak**. Naša studija ukazuje na to da bolesnici sa STEMI, sa ranim početkom VF i tVT, lečeni primenom pPKI i sa visokim nivoom BNP, imaju statistički značajno višu stopu mortaliteta u odnosu na bolesnike sa nižim nivoom BNP.

Ključne reči:
biomarkeri; mortalitet; perkutana koronarna intervencija; prognoza; infarkt miokarda sa st elevacijom; tahikardija, ventrikulska; fibrilacija komora.

Introduction

Ventricular fibrillation (VF) and sustained ventricular tachycardia (sVT) often occur in the acute phase of myocardial infarction (MI) with ST-segment elevation (STEMI) [1, 2] and significantly increase intrahospital mortality [3, 4]. Patients who were treated with a primary percutaneous coronary intervention (pPCI) and who survived sVT and VF in the first 48 hrs after STEMI, in most studies, had similar results of long-term prognosis compared to those patients without sVT and VF during the same period after STEMI [5, 6]. Therefore, current guidelines on STEMI treatment do not recommend implantation of cardioverter defibrillators (CD) in patients with sVT and VF within the first 48 hrs after STEMI, and there is no evidence to support the use of CD in such circumstances [7, 8].

An elevated level of B-type natriuretic peptide (BNP) may indicate the presence of acute heart failure regardless of the absence of heart failure clinical signs [9]. BNP emerged as a helpful laboratory finding in the diagnosis of heart failure in patients with acute coronary syndrome (ACS) [10]. Given that the elevated BNP level in ACS is associated with left ventricular dysfunction, the prognostic significance of serum BNP level on mortality is an independent risk factor [11]. Previous studies showed that the BNP level on the hospital admittance was predictive for short-term mortality more significantly than clinical assessment like Killip classification and Thrombolysis in Myocardial Infarction (TIMI) risk score in patients with STEMI treated with pPCI [12, 13].

Based on the studies conducted so far, we aimed to estimate the prognostic significance of life-threatening ventricular arrhythmias occurring within the first 48 hrs after STEMI for intrahospital and six-month mortality.

Furthermore, having in mind that most studies have not associated the relationship between early onset of sVT and VF during the first 48 hrs of STEMI and six-month mortality, we aimed to investigate the association of MI marker creatine kinase-MB fraction (CK-MB), heart failure marker – BNP and systemic inflammation factor – C-reactive protein (CRP) with early sVT and VF onset and its repercussion on six-month mortality in STEMI patients.

Methods

This retrospective study included 971 consecutive patients with STEMI who underwent pPCI and survived within the maximum ischemic time of 24 hrs. All patients were treated in the single university center with the maximal regard of the current guidelines for the treatment of STEMI patients. The cohort represented consecutive patients treated in a period of ten years from January 2008 to January 2018 at the Clinic for Urgent Internal Medicine of the Military Medical Academy in Belgrade, Serbia. The study was approved by the Ethics Committee of the Military Medical Academy (No. 76/2023, from October 12, 2023).

Patients were on continuous echocardiography monitoring during the first 48 hrs from admission to the intensive care unit. VF and sVT were detected out of the hospital (in the ambulance) and during the first 48 hrs of hospitalization and were treated promptly with asynchronous direct current (DC) shock, cardiopulmonary reanimation, and amiodarone intravenously. All patients who did not have contraindications were treated with oral beta-blockers from admission.

Echocardiography measurements of left ventricle ejection fraction and wall motion score index were performed by the independent, experienced echocardiographer at discharge, usually 4–6 days after admission. Clinical assessments were performed one and six months after infarction at the ischemic disease outpatient facility.

Laboratory tests

Glycemia was measured on admission from the venous blood samples using the commercial Dimension® Clinical Chemistry System [reference range (RR): 3.9 mmol/L–5.6 mmol/L]. Blood samples for extended-range

CRP were taken twice in the morning of two consecutive days from admission. CRP was determined in the serum of patients using the fully automated electrochemiluminescent assay by Siemens IMMULITE 2000 Immunoassay System (Siemens Healthcare Diagnostics, Deerfield, IL, USA), (normal values < 3 mg/L). CK-MB was determined in the serum of patients by the immunoinhibition method on the commercial Dimension® Clinical Chemistry System, on admission and every 8 hrs. During the first 48 hrs, normal values (< 21 units/L) were detected. BNP was determined in plasma samples on the commercial ADVIA Centaur analyzer (Siemens Medical Solutions, Fernwald, Germany) using direct chemiluminescence immunoassay (normal values < 100 pg/mL). Patients with a total cholesterol concentration greater than 5.2 mmol/L were classified as having hypercholesterolemia.

The study is retrospective, and we did not have all the data for every patient. However, this lack of data for individual variables in patients is in a statistically acceptable range of 0.3-3.2%.

Results

During the first 48 hrs from admission, 108 (11.1%) patients had life-threatening arrhythmias, of which 75 (69.4%) had VF, and 33 (30.6%) had sVT, treated with DC shock and intravenous amiodarone. One-fourth of the patients had VF/sVT before pPCI. The basic characteristics of the patients are presented in Table 1. Interestingly, there was no difference between the age, gender, risk factors, infarct-related artery, presence of multivessel disease, and reinfarction between patients with and without early onset life-threatening arrhythmias. Patients with VF/sVT were more often present in the earlier presenter's group, had some degree of decompensation on admission, and less often had TIMI-3 flow after pPCI. Patients with life-threatening arrhythmias did not have a lower incidence of ST-segment resolution after pPCI, and there was a similar distribution of presumably new Q waves on the electrocardiographic findings on admission in both groups.

Table 1

Demographic and clinical characteristics of patients

Parameters	Ventricular fibrillation or sustained ventricular tachycardia during the 48 hrs from admission		
	no (n = 863)	yes (n = 108)	*p*
Age (years)	63 ± 12	62 ± 11	0.696
Elderly			
< 70	607 (88.6)	78 (11.4)	0.738
≥ 70	256 (89.5)	30 (10.5)	
Gender			
female	254 (89.8)	29 (10.2)	0.654
male	609 (88.5)	79 (11.5)	
Atherosclerotic risk factors			
arterial hypertension			
yes	615 (89.0)	76 (11.0)	
no	243 (88.7)	31 (11.3)	0.910
missing data	5 (0.6)	1 (0.9)	
active smoking			
yes	403 (88.4)	53 (11.6)	
no	374 (89.3)	45 (10.7)	0.748
missing data	86 (9.7)	10 (9.3)	
diabetes mellitus			
yes	224 (89.2)	27 (10.8)	0.907
no	639 (88.8)	81 (11.2)	
hypercholesterolemia			
yes	409 (88.9)	51 (11.1)	
no	309 (87.8)	43 (12.2)	0.658
missing data	145 (16.8)	14 (13.0)	
Total ischemic time			
< 4 hrs	382 (91.4)	36 (8.6)	
≥ 4 hrs	467 (86.8)	71 (13.2)	0.030
missing data	14 (1.6)	1 (0.9)	
Killip class on admission			
1	126 (83.4)	25 (16.6)	
> 1	734 (89.8)	83 (10.2)	0.034
missing data	3 (0.3)		
IRA			
LAD	359 (87.3)	52 (12.7)	
RCX	129 (87.8)	18 (12.2)	0.259
RCA	375 (90.8)	38 (9.2)	

Table 1 (continued)

Parameters	Ventricular fibrillation or sustained ventricular tachycardia during the 48 hrs from admission		
	no (n = 863)	yes (n = 108)	*p*
TIMI flow before pPCI			
0/1	759 (88.8)	96 (11.2)	
2/3	99 (90.0)	11 (10.0)	0.880
missing data	5 (0.6)	1 (0.9)	
TIMI flow after pPCI			
< 3	131 (82.9)	27 (17.1)	
3	725 (90.1)	80 (9.9)	0.012
missing data	7 (0.8)	1 (0.9)	
Multivessel disease			
yes	527 (88.3)	70 (11.7)	
no	325 (89.8)	37 (10.2)	0.526
missing data	11 (1.3)	1 (0.9)	
Previous infarction			
yes	121 (89.6)	14 (10.4)	
no	737 (88.8)	93 (11.2)	0.883
missing data	5 (0.6)	1 (0.9)	
Early ST-segment resolution			
yes	525 (89.0)	68 (11.0)	0.915
no	308 (88.5)	38 (11.5)	
missing data	30 (3.5)	2 (1.9)	
New Q waves on admission			
yes	376 (90.0)	42 (10.0)	
no	467 (87.6)	66 (12.4)	0.303
missing data	20 (2.3)		
Implantation of stent in IRA			
yes	744 (88.5)	97 (11.5)	0.369
no	119 (91.5)	11 (8.5)	
Use of GP inhibitors during pPCI			
yes	245 (83.1)	50 (16.9)	
no	616 (91.5)	57 (8.5)	< 0.001
missing data	2 (0.2)	1 (0.9)	

IRA – infarct-related artery; LAD – left anterior descending; RCX – ramus circumflex; RCA – right coronary artery; TIMI – Thrombolysis in Myocardial Infarction; pPCI – primary percutaneous coronary intervention; GP – glycoprotein.
All values are expressed as numbers (percentages) except for age which is shown as mean ± standard deviation.

Several biomarkers were determined, and their significance was compared between patients with and without VF/sVT 48 hrs after admission. Admission glycemia was available in 97.6% and 96.3%, maximum CRP in 69.5% and 78.7%, maximum CK-MB in 95.0% and 93.5%, and BNP in 52.7% and 47.2% of patients, without and with VF/sVT during the 48 hrs, respectively.

The boxplots of biomarkers are presented in Figure 1. Results are shown as median (min-max). Patients with VF/sVT, as compared to those without, had significantly higher following values: admission glycemia [8.8 mmol/L, (7.1–10.9 mmol/L) vs. 7.8 mmol/L (6.6–9.9 mmol/L), $p = 0.006$, respectively], maximum CRP during the 48 hrs period [32.0 mg/L (12.5–78.0 mg/L) vs. 17.4 mg/L (8.1–49.5 mg/L), $p = 0.003$, respectively], maximum CK-MB during 48 hrs [317.0 IU/L (170.0–454.0 IU/L) vs. 172.0 IU/L (93.0–301 IU/L), $p < 0.001$, respectively], and BNP after 24 hrs from admission [347.3 pg/mL (144.4–708.8 pg/mL) vs. 221.0 pg/mL (108.6–400.0 pg/mL), $p = 0.012$, respectively].

The Kaplan-Meier curves of six-month all-cause mortality according to the occurrence of VF/sVT at 48 hrs are presented in Figure 2. Intrahospital mortality was significantly higher in patients with VF/sVT at 48 hrs after STEMI compared to patients without VF/sVT (14.8% vs. 5.7%, $p = 0.001$, respectively). The six-month mortality rate was 15.7% and 6.8% (log-rank $p = 0.001$) in patients with VF or sVT at 48 hrs after STEMI compared to patients without malignant arrhythmias, respectively. Left ventricle ejection fraction and wall motion score index at discharge were also significantly lower in patients with VF/sVT at 48 hrs after STEMI compared to patients without arrhythmias [44.8% vs. 47.6% ($p = 0.007$); 1.50 (1.28–1.75) vs. 1.37 (1.19–1.56), ($p < 0.001$), respectively].

The receiver operating characteristic (ROC) curves of BNP and CRP depending on the presence/absence of VF/sVT at 48 hrs after STEMI are presented in Figure 3.

BNP had higher accuracy in the prediction of six-month mortality than maximum CRP blood level in patients without VF/sVT at 48 hrs. However, in patients with early onset ma-

lignant arrhythmias, BNP had lower accuracy for the prediction of six-month mortality and CRP values had almost the same accuracy [area under curve (AUC) for BNP: 0.843 (0.806–0.875) in absence of VF/sVT vs. 0.732 (0.588–0.845) in the occurrence of VF/sVT; $p = 0.308$ and AUC for maximum CRP: 0.746 (0.709–0.780) in absence of VF/sVT vs. 0.743 (0.636–0.831) in the occurrence of VF/sVT; $p = 0.975$]. Admission glycemia had a much lower predictive value in both groups of patients compared to BNP and CRP [0.705 (0.628–0.781), ($p < 0.001$) and 0.662 (0.521–0.803), respectively ($p = 0.046$)]. Maximum CK-MB levels were not predictive for six-month all-cause mortality in either of the groups.

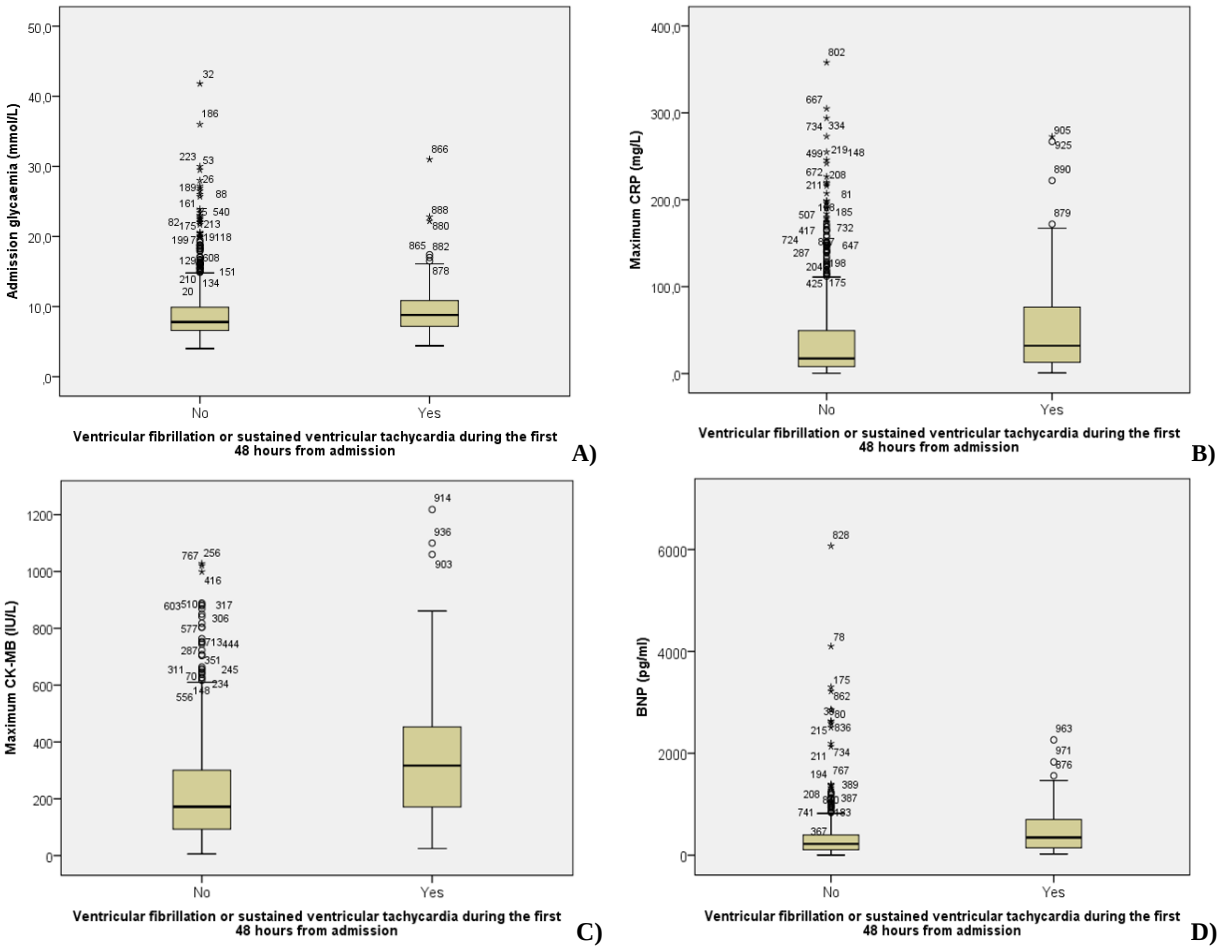


Fig. 1 – A) Admission glycemia; B) Maximum C-reactive protein (CRP); C) Maximum creatine kinase MB fraction (CK-MB); D) B-type natriuretic peptide (BNP) levels in patients with (Yes) ventricular fibrillation (VF) or sustained ventricular tachycardia (sVT) compared to the patients without (No) VF/sVT, during the first 48 hrs from admission.

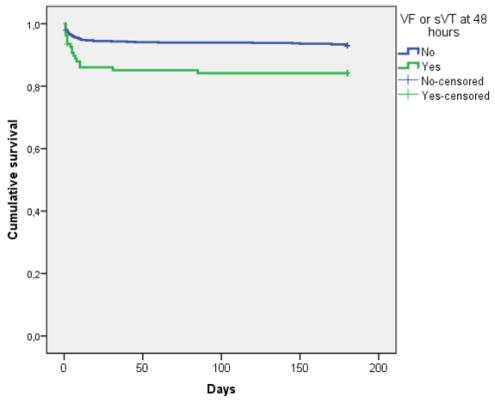
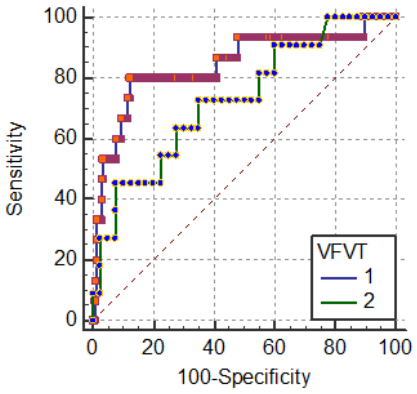
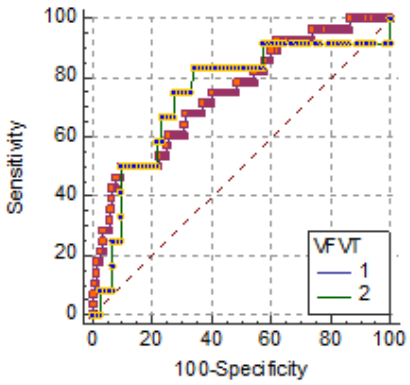


Fig. 2 – Kaplan-Meier curve of six-month survival regarding the presence (Yes) or absence (No) of ventricular fibrillation (VF) or sustained ventricular tachycardia (sVT) in the first 48 hrs from admission (log-rank $p = 0.001$).



A)



B)

Fig. 3 – The receiver operating characteristic curves for the prediction value of A) BNP in the presence (green line) and absence (blue line) of VF/sVT and B) max CRP in the presence (green line) and absence (blue line) of VF/sVT for six-month all-cause mortality.
BNP – B-type natriuretic peptide; VF – ventricular fibrillation; sVT – sustained ventricular tachycardia; CRP – C-reactive protein; z – z statistic of the test. The difference between the area under the curve (AUC) for BNP for patients with and without VF/sVT was Delta = 0.112, z = 1.019, *p* = 0.308. The difference between AUC for max CRP for patients with or without VF/sVT was Delta = 0.003, z = 0.031, *p* = 0.975.

Discussion

During the ten-year follow-up of consecutive STEMI patients treated with pPCI, we observed a greater intrahospital and six-month mortality among the patients who had VF/sVT within the first 48 hrs of hospital admission.

Patients with VF/sVT within the first 48 hrs had more often elevated markers of poor prognoses, such as hyperglycemia, CK-MB, BNP, and CRP.

Elevated levels of BNP and CRP proved to be good predictors of two-month mortality, and BNP showed greater predictive precision for this outcome [14]. Current guidelines for STEMI are based on the results of previous studies that VF which occurred during the first two days of STEMI are insignificant, regarding the long-term prognosis in case the patient survives until the discharge; no implantable CD efficacy has been demonstrated for prevention of sudden death [7].

However, most data concerning the prognostic significance of the early onset of VF/sVT for long-term outcomes was obtained during or even before the pPCI era. A few recent studies assessed VF/sVT in patients with STEMI treated with pPCI. The most important studies were Primary Angioplasty in Myocardial Infarction (PAMI) and APEX AMI [15, 16]. The APEX AMI study had the longest follow-up period, with 5,745 patients included. However, the patients were admitted to a hospital after the first six hours of STEMI, and those who had isolated posterior STEMI were excluded. Moreover, follow-up was limited to 90 days. The PAMI study assessed one-year survival, and 3,065 patients were included. At the same time, patients with chronic kidney disease, cardiogenic shock, and patients with contraindications for antithrombotic therapy were excluded.

Our study included all patients admitted to the hospital with an indication for pPCI during the period of ten years. The analysis did not exclude the most severe categories of patients, such as the patients with pre-hospital reanimation. Considering the profile of patients included in our study, differences between frequencies of malignant arrhythmias in our study (11.1%), the PAMI study (4.3%), and the APEX AMI study (5.7%) can be explained.

In research by De Jong et al. [17], 341 patients with VF and STEMI and 292 STEMI patients without VF were followed up. Demographic and infarct-related features were comparable in both groups. The follow-up median was three years. In conclusion, patients who survive the first month after primary VF have a similar prognosis to STEMI patients without VF. This is the first study that addresses this issue in the era of reperfusion therapy with pPCI.

Based on the previous studies, routine use of CD for all STEMI patients treated with pPCI and with early onset of VF/sVT is not indicated [7].

The purpose of the HORIZONS AMI [18] trial was the assessment of the risk factors and outcome of VF before and during pPCI in patients with STEMI. In this study, 5,537 patients with STEMI were included. In total, 410 patients had VF before and 88 during pPCI. Through the middle follow-up period of 4.2 years, 1,196 patients died. The logistic regression model identified younger age, anterior infarct, Killip class > 1 at the moment of hospital admission, pre-PCI fibrinolysis with TIMI flow 0–1 as significantly related to VF before pPCI, while inferior infarct thrombolysis before pPCI with TIMI flow 0–1 and Killip class > 1 at the moment of hospital admission was significantly related to VF during pPCI. In comparison, patients with VF before or during pPCI had significantly increased mortality during the first 30 days. In patients with VF before or during pPCI who survived at least 30 days, there was no increase in long-term mortality.

The aim of this investigation was the identification of a potential subgroup of STEMI patients with recorded VF/sVT during the first 48 hrs and treated with pPCI, which might have potential benefit from the implantation of CD.

Study limitations

A large number of patients was included in this monocentric study over a long period of ten years. During that period, the basic indicator of myocardial necrosis, high-sensitivity troponin, was used in almost all patients. However, different assays from different manufacturers with different reference values were used, and the concentration of this parameter could not be adequately statistically processed.

Conclusion

Previous studies did not find a relationship between VF and sVT onset during the first 72 hrs and increased mortality in patients with STEMI who underwent pPCI. Our study indicates that STEMI patients with early onset of VF and sVT, treated with pPCI, with a high BNP level, have a statistically significantly higher mortality rate compared to patients with a lower BNP level.

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