

Temporal Trends in Prognosis of Patients with Acute Coronary Syndrome Complicated by Ventricular Tachyarrhythmia

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April 15, 2021

Abstract

Objectives: To evaluate clinical characteristics and prognosis of patients presented with ventricular tachyarrhythmia (VTA) during the course of acute coronary syndrome (ACS) and to analyze it according to period of presentation. **Background:** VTA is an infrequent yet serious complication of ACS. There is limited data regarding the incidence and prognostic implications of VTA in the last decade as compared with the previous decade. **Methods:** We evaluated clinical characteristics, major adverse cardiovascular events, short and long- term mortality of patients hospitalized with ACS who were enrolled in the Acute Coronary Syndrome Israeli Survey (ACSIS) during the years 2000-2016. Patients were classified into three groups: no VTA, early VTA ([?]48h of onset) and late VTA (>48h of onset). Data were analyzed according to decades of presentation (current decade vs. previous decade). **Results:** The study population comprised 15,200 patients. VTA occurred in 487 (3.2%) of patients. Early VTA presented in 373/487 (77%) patients and late VTA in 114/487 (23%) patients. VTA's, occurring in ACS patients were associated with increased risk of in-hospital, 30-days, 1-year and 5-year mortality rates during both early and late periods in compared with no VTA. Moreover, late VTA was associated with the highest mortality rate with up to 65% in 5-year follow up ($p<0.001$). Nevertheless, late VTA was associated with lower mortality rate in the current decade (2008-2016) compared with last decade (2000-2006). **Conclusions:** Any VTA following ACS was associated with high short and long-term mortality rate. However, over the past decade there has been a significant improvement in survival rates, especially in patients with late VTA. This may be attributed to early and invasive reperfusion therapy, implantable cardioverter defibrillator implantation and better medical treatment.

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No conflict of interest and no relationship with industry exists

Abstract:

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Methods: We evaluated clinical characteristics, major adverse cardiovascular events, short and long-term mortality of patients hospitalized with ACS who were enrolled in the Acute Coronary Syndrome Israeli Survey (ACSIS) during the years 2000-2016. Patients were classified into three groups: no VTA, early VTA (≤ 48 h of onset) and late VTA (> 48 h of onset). Data were analyzed according to decades of presentation (current decade vs. previous decade).

Results: The study population comprised 15,200 patients. VTA occurred in 487 (3.2%) of patients. Early VTA presented in 373/487 (77%) patients and late VTA in 114/487 (23%) patients. VTA's, occurring in ACS patients were associated with increased risk of in-hospital, 30-days, 1-year and 5-year mortality rates during both early and late periods in compared with no VTA. Moreover, late VTA was associated with the highest mortality rate with up to 65% in 5-year follow up ($p < 0.001$). Nevertheless, late VTA was associated with lower mortality rate in the current decade (2008-2016) compared with last decade (2000-2006).

Conclusions: Any VTA following ACS was associated with high short and long-term mortality rate. However, over the past decade there has been a significant improvement in survival rates, especially in patients with late VTA. This may be attributed to early and invasive reperfusion therapy, implantable cardioverter defibrillator implantation and better medical treatment.

Key words: Ventricular tachyarrhythmia, all-cause mortality, acute coronary syndrome, NSTEMI, STEMI, risk-factors.

What is already known about this tt does this article add?

What is known about this topic?

VTA is rare yet serious complication of acute coronary syndrome (ACS) and has adverse implications on in-hospital and long-term mortality based on older trials. VTA associated with acute myocardial infarction (AMI) are classified as early (within the first 48 hours) which are the most frequent cause of AMI-related death and late (after 48 hours), usually associated with ventricular dysfunction. Limited data exists regarding the association between VTA observed during AMI hospitalization and short and long-term mortality.

What does this study contribute to the literature?

In the current study, majority of VTA occurred during the first 48 hours of ACS. The incidence of both early and late VTA did not change significantly during the years 2000-2016, suggesting it was not related to medical treatment. The overall prognosis of ACS patients improved in the last decade and the most prominent improvement was seen in those who had late VTA.

Introduction

Ventricular tachyarrhythmia (VTA) especially sustained ventricular tachycardia and ventricular fibrillation, is an infrequent yet serious complication of acute coronary syndrome (ACS). Prior studies reported that VTA complicates 2-8% of ACS cases and has adverse implications on in-hospital and long-term mortality (1, 2). Early VTAs occur in the first 48 hours of acute myocardial infarction (AMI) and are the most frequent cause of AMI-related death (3). Late VTAs i.e. > 48 hours of AMI onset are usually associated with ventricular dysfunction (4). Over the past decade, major advances in the treatment of patients with AMI have occurred and led to improved survival (5). Currently, however, there is limited data regarding the incidence and temporal trends over recent years in the outcomes of patients presenting with VTA complicating ACS. Moreover, limited information exists regarding the association between VTA observed during ACS hospitalization to short and long-term mortality. This is despite overall enhanced therapy and improved survival among ACS patients. Therefore, the purpose of the current study was to evaluate temporal trends of clinical characteristics and outcomes over the last two decades (2000-2016) among ACS patients presenting with and without VTA who were enrolled in the Acute Coronary Syndrome Israeli Survey (ACSIS) survey.

Methods

Study population

The present study is a cohort data analysis of patients who were enrolled prospectively in the ACSIS from 2000 to 2016. Details of ACSIS have been previously reported (6). In brief, this survey is conducted biennially over a 2-month period among ACS patients admitted to coronary care units and cardiology wards in all 27 public hospitals in Israel.

Patient management was at the discretion of the attending physicians. The diagnosis of AMI and ST-segment elevation MI (STEMI) or non-ST-segment elevation MI (NSTEMI), was made by the attending cardiologist according to pre-specified survey criteria based on accepted guidelines. In total 15,200 patients were enrolled in our study. The patients were grouped according to the occurrence of ventricular arrhythmias during the course of index AMI. Data included baseline demographics, medical history, hospital course, procedures, complications, and outcome based on hospital's charts. Additional data regarding health status, adverse events and medication adherence were collected from the patients via follow-up calls and from outpatients' medical records one month after hospital discharge. Mortality rates were determined for all patients from hospital and out-patient charts and by matching their identification numbers with the Israeli National Population Register. In-hospital, one year, and five-year all-cause mortality was assessed for the absence of VTA, early VTA and late VTA according to the periods of presentation.

Definitions and endpoints

The diagnosis of VTA, sustained ventricular tachycardia or ventricular fibrillation was based on electrocardiogram (ECG) or continuous monitor strips. Sustained ventricular tachycardia was defined as a series of abnormally shaped QRS complexes longer than 120 milliseconds, with a rate 100-250 beats/minute, lasting longer than 30 seconds or requiring electrical cardioversion due to hemodynamic collapse. Ventricular fibrillation was defined as rapid, very irregular rhythm with indiscernible P waves or QRS. Patients were classified into three groups: no VTA; early VTA ([?]48h of onset) and late VTA (>48h of onset). Survey periods were divided to early decade (2000-2006) vs. late decade (2008-2016). Primary endpoints were 30-day, 1-year and 5-year mortality rate. Secondary endpoints included 30-day major adverse cardiac events (MACE) (all-cause mortality rate, re-infarction, stent thrombosis and urgent revascularization). Left ventricular ejection fraction (LVEF) was graded according to echocardiography performed at admission in each center.

Statistical methods

Demographic, clinical features and the use of in-hospital therapies were reported for all study participants. Multiple logistic regression adjustments for age, gender, diabetes mellitus, chronic renal failure and heart

failure and for survey periods was performed to assess the adjusted odds ratio (OR) and 95% confidence interval (CI) of in and out of hospital complications and 30-day, 1 and 5-year mortality rate associated with VTA at any time during and after the admission for ACS. The cumulative probability of all-cause mortality rate was graphically displayed using the Kaplan–Meier method and compared using the log-rank test. In order to evaluate the independent association of VTA with the 5-year all-cause mortality rate outcome, a Cox proportional hazards model was constructed adjusting for survey period. We employed an interaction-term analysis to examine whether the risk of 5-year mortality rate associated with VTA was different in the early period as compared with the late period. Statistical significance was accepted for a 2-sided $p < 0.05$. Statistical analysis was performed using the R Statistical Package (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline characteristics

The study population comprised of 15,200 patients with ACS. Of them 11682 (77%) were males, 5383 (35%) suffered from diabetes mellitus 8894 (59%) had a history of arterial hypertension, 9757 (64%) had dyslipidemia and 6931 (46%) presented with STEMI. Patient's baseline characteristics are presented in Table 1.

Ventricular tachyarrhythmia characteristics

Four hundred eighty-seven patients (3.2 %) had VTA during their hospitalization. Among those patients, 373/487 (77%) had early VTA and 114/487 (23%) had late VTA. The incidence of both types of VTA's remained the same in the past 15 years as shown in Figure 1. Patients with late VTA were older (65±14 vs. 64±13, $p < 0.001$) and had significantly higher incidence of co-morbidities and coronary risk factors such as diabetes mellitus, arterial hypertension, as well as known coronary artery disease, and chronic renal failure as shown in Table 1.

Outcome

Rate of MACE was higher in late VTA then in early and non-VTA (49% vs. 23% vs. 8%, respectively, $p < 0.001$). As shown with logistic regression model the presence of late VTA was associated with three folds' higher ratios for 30 days MACE ($p < 0.001$), Figure 2. In-hospital and 1-year mortality rate were also higher in the presence of late VTA as compared with no VTA [HR 27.44 (95% CI 17.56- 42.49) and 9.78 (95% CI 6.57- 11.18), respectively, $p < 0.001$]. Even after multivariate logistic regression for confounders the presence of early VTA and late VTA, were independently associated with increased risk of in-hospital mortality rate [OR 9.65 (95% CI 7.0-13.13) and 27.64 (95% CI 17.56-42.49), respectively, $p < 0.001$], and early post-discharge mortality rate [OR 8.75 (95% CI 5.98-12.24) and 22.6 (95% CI 14.5-35.62), respectively, $p < 0.001$]. Moreover, multivariable Cox proportional hazard analysis including baseline potential confounders confirmed that 5-year mortality rate was also higher in late VTA then in early and non-VTA (HR 8.27 vs. 2.65, for late and early VTA, respectively 95% CI 2.05-3.42).

Late vs. Early period

The 1 and 5-year all-cause mortality rate was lower during the late period as compared with the early period for patients with no VTA, early VTA and late VTA (8% vs 10%, 20% vs 25% and 37% vs 65%, all log-rank $p < 0.001$, respectively for 1 year) and (20% vs 23%, 26% vs 29% and 45% vs 75%, all log-rank $p < 0.001$, respectively for 5 years) as shown in Figure 3 and 4. Moreover, the late period was associated with lower all-cause mortality rates for in-hospital, 1 year and 5 years mortality rate (OR 0.56, 0.66 and 0.82, $p < 0.001$, respectively).

In the early period ICD was implanted during hospitalization in 15 (0.2%) patients with no VTA, 3 (1.4%) patients with early VTA and 5 (8%) with late VTA ($p < 0.001$). In the late period in hospital implantation of ICD was performed in 25 (0.4%), 8 (5%) and 0 patients, respectively ($p < 0.001$).

In our study during early period chronic treatment with beta blockers was administered to 34%, 24% and 42.5% of patients with no VTA, early VTA and late VTA respectively, $p=0.018$; beta blockers at discharge were prescribed to 78%, 72% and 51% of patients respectively, $p<0.001$

During the late period 38.5%, 35% and 42% of patients with no VTA, early VTA and late VTA, respectively, used beta blockers chronically, $p=0.6$ and 80.5%, 81.5%, 73% of patients, respectively, were discharged with beta blockers, $p=0.4$ Chronic angiotensin-converting-enzyme inhibitor (ACEI) treatment in early period was used in 26%, 31% and 22% of patients with no VTA, early VTA and late VTA $p=0.8$; ACEI after discharge were prescribed to 61%, 61.5% and 57%, respectively, $p=0.9$

During the late period chronic ACEI treatment was administered to 32%, 32%, 24% of patients with no VTA, early VTA and late VTA respectively, $p=0.08$; ACEI in discharge were prescribed to 67%, 66%, 47% of patients respectively, $p=0.018$

Discussion

In the current study, VTA occurred in roughly 3% of ACS patients admitted to the hospital with the majority (77%) of those arrhythmias occurred during the first 48 hours of ACS. Moreover, the incidence of both early and late VTA did not change significantly during the years 2000-2016, suggesting it was not related to medical treatment.

Previous data on prognostic significance of VTA is controversial. In the HORIZONS-AMI Trial (7) there was no significant difference in MACE and 3-year mortality rate in patients with or without VTA that occurred after primary percutaneous coronary intervention (PCI). Another recent study, found that in patients with STEMI that survived out of hospital cardiac arrest due to VTA and underwent primary PCI, the 1-year mortality was equal to those without out of hospital cardiac arrest (8). On the other hand, in the MILIS study (9) the in hospital mortality rate was significantly increased by VTA, especially late VTA, causing cardiac arrest during ACS hospitalization, although there was no difference in mortality rate in the 32-month follow up as compared with patients with no VTA. In APEX AMI trial (10), pre and post primary PCI VTA were also shown to be associated with significantly increased 90 days mortality. Piccini et al. (11) studied a large population of 9000 patients with STEMI and NSTEMI undergoing PCI. In their study, the rate of early VTA was 5.2% and it was also related to increase mortality risk by 4.4 folds as compared with no VTA. Our data is in accord to the aforementioned trials suggesting that VTA occurrence during the course of ACS is not benign. Short and long-term mortality rate was increased dramatically by the presence of early and especially late VTA as compared with no VTA. This was consistent even after adjustment for multiple confounders. In the logistic regression analysis model the presence of late VTA was associated with 27 folds' increase of in hospital mortality, 10 folds increased one-year mortality and 8 folds increased 5 years mortality rate. The proposed reason why late VTA carries an increased risk of death might be its association with pump failure and hemodynamic deterioration rather than arrhythmic death (12, 13).

Interestingly, although the overall prognosis of ACS patients improved in the last decade (14) as well as in our study, the most prominent improvement in our study was seen in those who had late VTA, as shown in Figures 3 and 4. Wider use of ACE inhibitors and beta blockers at discharge in the late VTA group, early reperfusion strategy, (15, 16), as well as wider use of implantable and wearable cardioverter defibrillators could explain our findings.

Limitations

Due to its observational non-randomized design, the current study is subject to limitations as described in detail previously (17). Thus, despite efforts to control for confounding factors by applying multivariate analysis, we cannot exclude unmeasured factors, which could have biased the results. Moreover, data regarding 5 years survival rate is limited in the late period with no long term data since the year 2016. Nevertheless, in spite of these limitations, the study in a multicenter nationwide survey with large study population and long term outcomes.

Conclusions

In summary, in this national, multicenter, contemporary “real life” setting, we did not observe any change in the rate of VTA. Nevertheless, any VTA following AMI was associated with high short and long-term mortality rate. However, over the past decade there has been a significant improvement in survival rates, especially in patients with late VTA that may be attributed to early and invasive reperfusion therapy, implantable cardioverter defibrillator implantation and better medical treatment.

This statement is to certify that all authors have seen and approved the manuscript

being submitted, have contributed significantly to the work, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to the *International Journal of Clinical Practice*.

The article is the Authors’ original work, has not received prior publication and is not under consideration for publication elsewhere.

All the authors report no relationships that could be construed as a conflict of interest.

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Table 1: Baseline characteristics by VTA presence

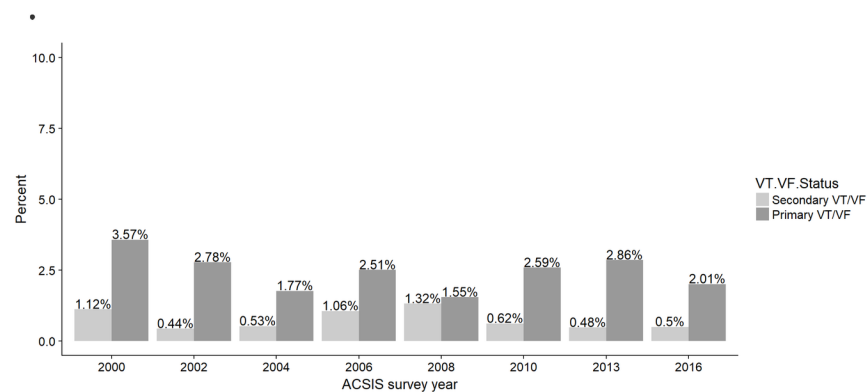
	No VTA N=14713	Early VTA N=373	Late VTA N=114	p-value
Age(\pm SD), years	64 \pm 13	60 \pm 12	65 \pm 14	<0.001
Male gender, %	11287 (77)	308(83)	87(76)	0.030
Weight (kg), (\pm SD)	79 \pm 15	80 \pm 17	83 \pm 17	0.162
Diabetes Mellitus, %	5256(36)	89(24)	38(33)	<0.001
Hypertension, %	8652(59)	171(46)	71(62)	<0.001
Dyslipidemia, %	9505(65)	195(53)	57(51)	<0.001
Past stroke/TIA, %	1186(8)	31(8)	5(4)	0.355
Prior Chronic Renal Failure, %	11612(11)	20(5)	120(17)	<0.001
Prior COPD, %	697(6)	23(7.9)	3(4)	0.455
Prior MI, %	4481(31)	102(28)	38(33)	0.360
Prior AP in 24 hours,%	5168(35)	77(21)	41(36)	<0.001
Prior CABG, %	1481(10)	15(4)	8(7.1)	<0.001
History of PCI, %	4058(28)	77(21)	28(25)	0.009
Heart failure, %	1144(8)	29(8)	15(13)	0.106
Family history of CAD,%	3466(25)	74(21)	31(29)	0.214
<i>Clinical Presentation</i>				

	No VTA N=14713	Early VTA N=373	Late VTA N=114	p-value
STEMI, %	6564(45)	289(78)	78(68)	<0.001
Heart Rate (mean±SD), bpm	80±20	87±29	89±24	<0.001
<i>Treatments</i>				
Primary	4458(30)	249(67)	53(47)	<0.001
Reperfusion, %				
Coronary angiography (till hospital discharge),%	9513(86)	224(89)	69(81)	0.215
PCI, %	5862(40)	89(24)	40(35)	<0.001
Emergency CABG,%	700(5)	11(3)	6(5)	0.250
Beta Blockers chronic, %	4664(36)	90(30)	38(42)	0.029
Beta Blockers at discharge, %	11347(79)	258(76)	55(62)	<0.001
<i>Outcome</i>				
MACE in 30 days, %	1173(8)	84(23)	56(49)	<0.001
All-cause mortality 30 days, %	625(4)	69(19)	49(43)	<0.001
All-cause mortality 1 year, %	1208(9)	76(23)	55(53)	<0.001
All-cause mortality 2 years, %	1596(13)	83(26)	60(59)	<0.001

VTA- Ventricular tachyarrhythmia, SD- standard deviation, PCI - percutaneous coronary intervention, CABG - coronary artery bypass grafting, STEMI -ST elevation myocardial infarction, CAD- coronary artery disease, MACE- major adverse cardiac events, TIA - transient ischemic attack, PAD- peripheral artery disease, COPD- chronic obstructive pulmonary artery

disease.

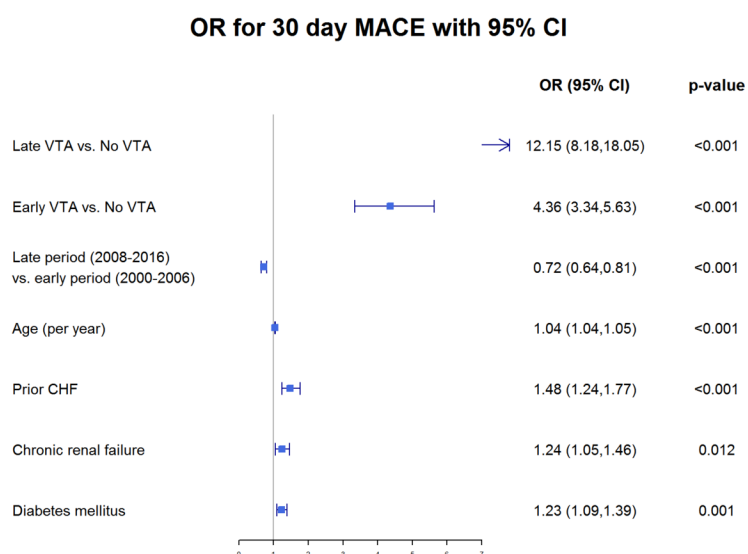
Figure 1. Trends in VTA during the years 2000-2016



Early VTA

Late VTA

Figure 2. Major adverse cardiac events (MACE) at 30 days for early and late VTA



*MACE- all-cause mortality rate, re-infarction, stent thrombosis and urgent revascularization

CI= confidence interval, OR= odds ratio

Figure 3. One-year survival rate according to period of presentation

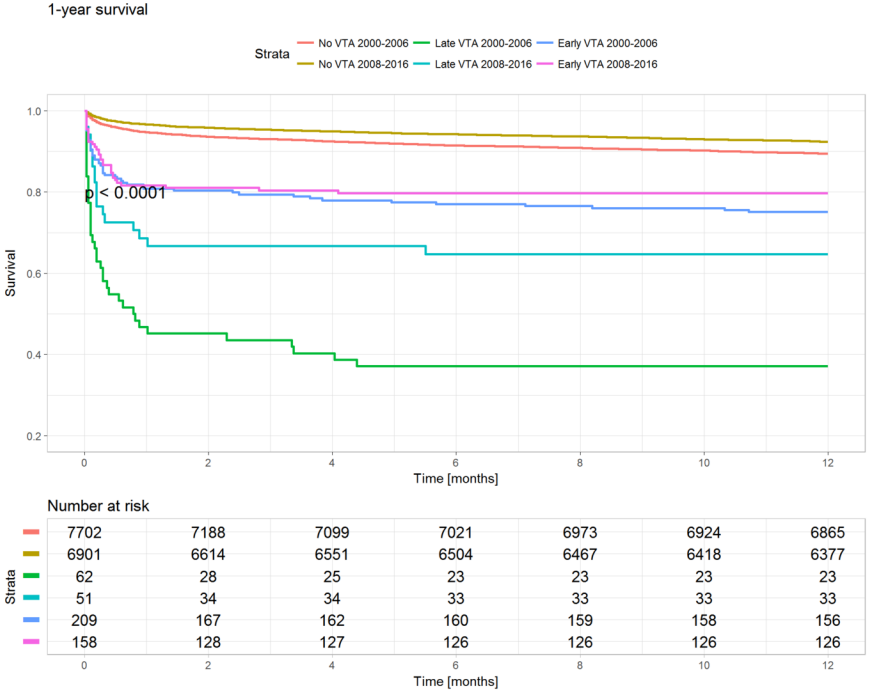


Figure 4. Five-year survival according to period of presentation

