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Review Article

Incidence and prognostic significance of atrial fibrillation in patients with tako-tsubo syndrome-systematic review and meta-analysis

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Abstract

Background: Tako-tsubo syndrome (TTs) is relatively young cardiovascular entity, being initially described in the 1991 by dr Hikaru Sato. Most patients with TTs are admitted to the hospital with the suspicion of acute coronary syndrome or present signs and symptoms typical for acute heart failure. Atrial arrhythmias are thought to complicate almost 10% of all TTs cases. The most prevalent among them is atrial fibrillation (AF). Our aim in this study was to systematically evaluate results of observational studies to assess the incidence and prognostic relevance of supraventricular tachyarrhythmias in TTs patients.

Methods: We performed systematic search of the Cochrane Central Register of Controlled Trials, PubMed, and EMBASE databases for research evaluating the incidence and prognostic relevance of atrial fibrillation(AF)/atrial flutter(AFl)/atrial tachycardia(AT) in patients hospitalized due to TTs. Odd ratio (OR) with a 95% confidence interval (CI) was estimated using a random effect model.

Results: 10 studies comprising 4183 patients were included. The incidence of atrial arrhythmias ranged between 7% to 33%. In our research, supraventricular tachyarrhythmias were associated with significant increased risk for all-cause death (OR 2.99; 95% CI: 2.36- 3.80; $p < 0.05$), intra-hospital mortality (OR 2.46; 95% CI: 1.30 – 4.63; $p < 0.05$) and long-term mortality (OR 3.01 95% CI: 2.33– 3.90; $p < 0.05$).

Conclusions: Our meta-analysis suggests that atrial arrhythmias are associated with an elevated risk for short and long-term adverse outcomes in patients with TTs.

Keywords: Takotsubo cardiomyopathy, Arrhythmias, Cardiac, Atrial fibrillation, Heart failure.

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Tako-tsubo syndrome (TTs) is relatively young cardiovascular entity, being initially described in the 1991 by dr Hikaru Sato. Unusual name of this disease originate from a Japanese octopus trap and relates to its' resemblance to the systolic shape of the left ventricle in the ventriculography (1). Most patients with TTs are hospitalized due to the suspicion of acute coronary syndrome (ACS), or present signs and symptoms typical for acute heart failure (2). In echocardiography they present impaired left ventricular systolic function with regional wall motion abnormalities exceeding beyond single epicardial coronary artery distribution with concomitant elevated cardiac damage biomarkers in laboratory tests (3). In coronary angiography no atherosclerotic plaques are seen or non-obstructive coronary disease is diagnosed. A vast majority of patients with broken heart syndrome report emotional or physical stress as a trigger. Primarily TTs was thought to be a transient disease, not bearing high risk for in- and out-hospital adverse outcomes. However, a clinical course of TTs might be complicated with a cardiogenic shock, acute pulmonary edema, malignant ventricular arrhythmias, supraventricular arrhythmias and thromboembolic events (4).

Apart from that, left ventricular (LV) systolic function might sustain chronically decreased. In 2019, Prasitlumkum et al. conducted systematic review and meta-analysis, in which they concluded that atrial fibrillation (AF) in patients with TTs was associated with an elevated risk of an overall mortality (5). We decided to conduct an update after publication several significant studies in this topic (Jesel et al. 2018; El-Battrawy et al. 2021; Martin Demiguel et al. 2019; Azevedo et al. 2018; Arcari et al. 2020; Schneider et al. 2018). What is more, our literature search will comprise screening of 3 databases: PubMed, EMBASE and Cochrane Central Register of Controlled Trials and will not be limited to English language publications. Apart from that we are not going to restrain to AF but also enclose other supraventricular arrhythmias.

Methods

The systematic review and meta-analysis were accomplished according to the PRISMA 2020 statement. Systematic electronic literature search was performed using Cochrane Central Register of Controlled Trials, PubMed, and EMBASE databases from inception to the January 2022, for studies evaluating prevalence and prognostic relevance of atrial fibrillation(AF)/atrial flutter(AFl)/atrial tachycardia(AT) in patients hospitalized due to Tako-Tsubo cardiomyopathy. We used search terms such as: "atrial fibrillation", „atrial flutter", „Tako Tsubo cardiomyopathy", „stress cardiomyopathy", „apical ballooning syndrome", „broken heart syndrome", „mortality" and „death". The search detail was (((atrial fibrillation) OR (atrial flutter)) AND ((((Cardiomyopathy, tako tsubo(MeSH Terms)) OR (Stress cardiomyopathy)) OR (apical ballooning syndrome)) OR (Broken heart syndrome))) AND ((mortality) OR (death)). We extended our search to the reference lists of the retrieved articles for potentially eligible trials, which had not been previously identified in the database search.

We restrained literature search to clinical studies, scientific session abstracts, oral presentations, and/or expert slide presentations. All items derived from abovementioned search strategy were investigated at the title and abstract level and potentially eligible studies were evaluated in full text to assess eligibility. We also tried to obtain accessory information lacking in original articles by a direct contact with the main authors. Newcastle-Ottawa Scale was used to estimate quality of the qualified studies (6). Our study was registered in PROSPERO register (CRD42022321095).

Study eligibility criteria: We qualified in our study trials in which patients: a) were adult (at least 18 years old); b) were diagnosed with TTs; c) had either history of supraventricular tachyarrhythmias (AF/AFl/AT) or new-onset of supraventricular tachyarrhythmias (AF/AFl/AT) during hospitalization due to an episode of TTs. We excluded studies in which results were based on national healthcare databases.

Data extraction: Independently two researchers (A.O and K.S) extracted data from each qualified study and potential discordant were resolved by discussion and consensus reached between A.O and K.S. We reported the study characteristics (publication year, study design, follow-up duration, and number of participants), patient demographics and clinical characteristics (type of TTs, presence of hypertension, diabetes mellitus, dyslipidaemia, current smoking, chronic kidney disease, obesity, coronary artery disease, chronic obstructive pulmonary disease or asthma, history of malignancy, underlying stressor), clinical presentation on admission (dyspnoea, chest pain, syncope, cardiac arrest), echocardiographic parameters and laboratory tests results, prevalence of AF/AFl/AT in-hospital events and mortality. Different TTs definitions were used in qualified articles (see supplementary material).

Data analysis: To synthesize the pooled odds ratios (ORs), we used 2 x 2 tables to extract data. ORs and 95% confidence intervals (CI) were calculated. The overall pooled prevalence and pooled ORs estimate were computed for the random-effects model, based on the inverse variance approach for measuring weight. Inconsistency index (I2 statistics) was used to assess the magnitude of heterogeneity among included studies, with I2 value >25%, 25–75%, <75% were taken as low, moderate, and high heterogeneity, respectively (7). We assessed publication bias by visual inspection of the funnel plot and further validated using Egger's regression test (8) and Begg's correlation test (9).

Results

We identified in the literature search 360 studies (figure 1). After the elimination of duplicates, non-relevant studies and analysis of studies on title and abstract levels, 37 studies were extracted for further full-text evaluation. Thereafter we eliminated eleven studies which used national healthcare databases, seven studies that did not report outcome of interest, five studies, which used identical databases, three trials which did not report mortality among patients with AF and one study which was an editorial article. Finally, 10 studies published in the period 2008-2021 were qualified in this research (10-19). Studies and patient's characteristics are summarized in table 1. The eligible studies encompassed a total of 4183 patients. Study participants

were predominantly female (range 81% to 100%) and their mean age ranged from 66.1 to 79 years. In our study, prevalence of atrial arrhythmias ranged between 7% to 33%.

Risk of bias: Using Newcastle Ottawa Scale risk of bias and quality of included studies were estimated (table 2).

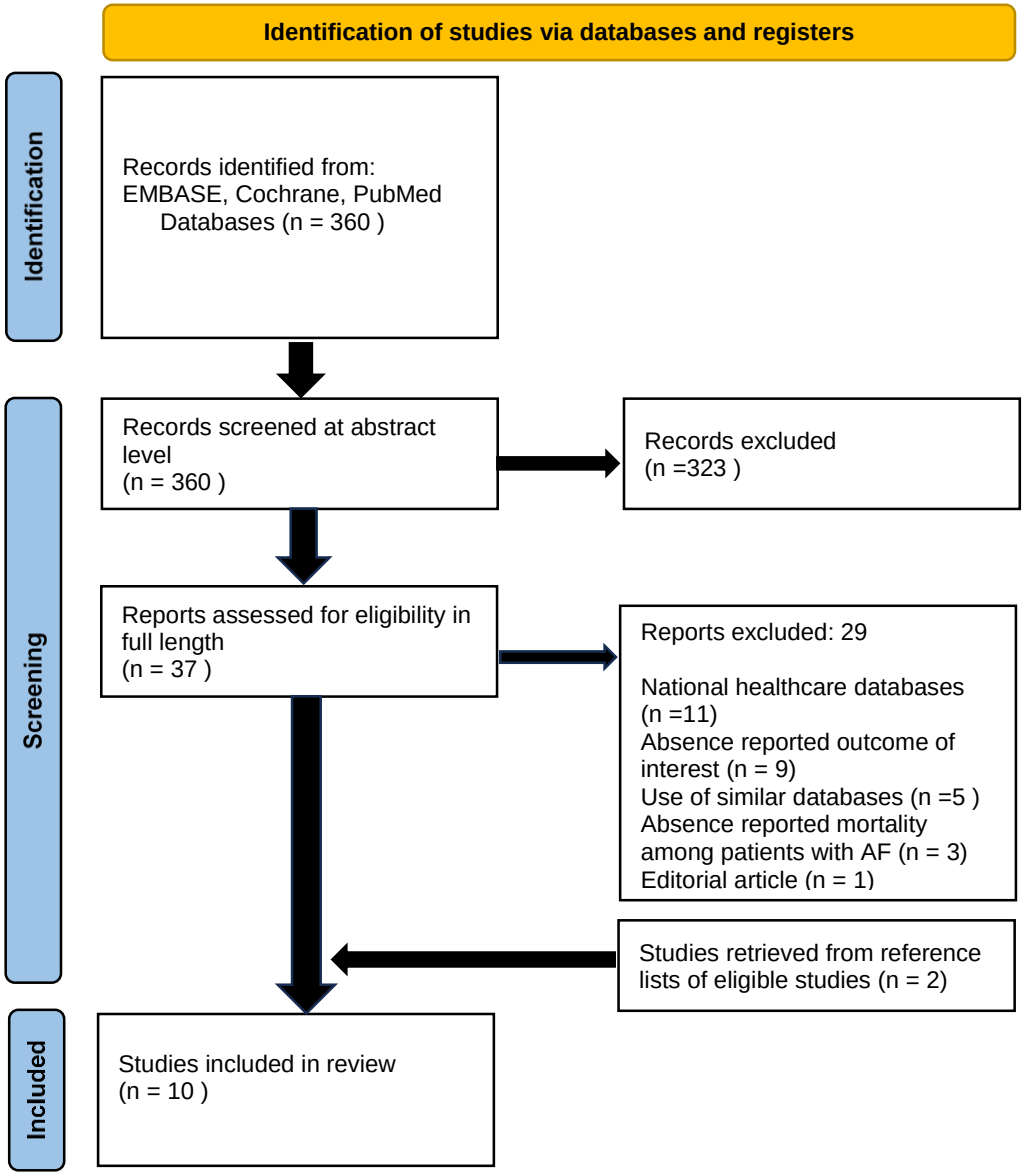

Figure 1. PRISMA flow diagram

All-cause death: There was an association between supraventricular tachyarrhythmias and all- cause death in patients with TTs (OR 2.99; 95% CI: 2.36- 3.80; $p < 0.05$). Forrest plot of odd ratio is presented at figure 2 and funnel plot of odd ratio is depicted at supplement figure 1. No heterogeneity among the included studies has been identified: I2 = 0 (95% CI: 0 – 46.01) and T2 = 0 (95% CI: 0 – 0.144). The sensitivity analysis presented no significant changes in the overall result of the meta-analysis. Even after excluding individual studies from the calculations, the overall result was still indicating correlation between supraventricular arrhythmias and all cause death in patients with broken heart syndrome and was in the range from 2.77 (95% CI: 2.10 – 3.66) to 3.07 (95% CI: 2.41 –3.92). No correlation has been found between effect sizes and standard errors Egger test: $p = 0.95$.

Intrahospital mortality: Into this sub-analysis 5 trials were included, comprising 809 patients. This subgroup analysis revealed that patients with supraventricular tachyarrhythmias have statistically significant higher risk for intrahospital mortality (OR 2.46; 95% CI: 1.30 – 4.63; $p < 0.05$). Forrest plot of odd ratio is depicted at supplement

figure 2. No heterogeneity among the included studies has been identified: I2 = 0 (95% CI: 0 – 55.64) and T2 = 0 (95% CI: 0 – 0.86. The sensitivity analysis showed that only after exclusion of Jesel et al.'s study, the overall result of this sub-analysis would turn into insignificant, p > 0.05. No correlation has been found between effect sizes and standard errors Egger test: P = 0.38.

Long-term mortality: Into this sub-analysis**,** 7 trials were included, comprising 3715 patients. This subgroup analysis also revealed that patients with supraventricular tachyarrhythmias have statistically significant higher risk for long-term mortality (OR 3.01 95% CI: 2.33– 3.90; p < 0.05). Forrest plot of odd ratio is presented at supplement figure 3 and funnel plot of odd ratio is depicted at supplement figure 4. No heterogeneity among the included studies has been identified: I2 = 0 (95% CI: 0 – 39.96) and T2 = 0 (95% CI: 0 – 0.09). The sensitivity analysis presented no significant changes in the overall result of this sub-analysis. Even after excluding individual studies from the calculations, the overall result was still indicating correlation between supraventricular arrhythmias and long-term mortality in patients with broken heart syndrome and was in the range from 2.74 (95% CI: 2.01–3.74) to 3.11 (95% CI: 2.39– 4.04). No correlation has been found between effect sizes and standard errors Egger's test: P= 0.19.

Table 1. Detailed characteristics of included studies

Author	Title	Country
Schneider B. (2018)	Ventricular Tachycardia and Atrial Fibrillation Complicating the Clinical Course of Tako-tsubo Cardiomyopathy: Results of the German Tako-tsubo Registry	Germany
Arcari L. (2020)	Incidence, determinants and prognostic relevance of dyspnea at admission in patients with Takotsubo syndrome: results from the international multicenter GEIST registry	Italy, Germany
Song B.G. (2010)	Clinical characteristics, ballooning pattern, and long-term prognosis of transient left ventricular ballooning syndrome	South Korea
Dib C. (2008)	Malignant Arrhythmia in Apical Ballooning Syndrome: Risk Factors and Outcomes	USA
Azevedo P.M. (2018)	Prevalence and prognostic impact of atrial fibrillation in patients with Takotsubo cardiomyopathy	Portugal
Martín-Demiguel I.(2019)	Prevalence and Significance of Interatrial Block in Takotsubo Syndrome (from the RETAKO Registry)	Spain
El-Battrawy I.(2016)	Impact of concomitant atrial fibrillation on the prognosis of Takotsubo cardiomyopathy	Germany
El-Battrawy I.(2021)	Impact of Atrial Fibrillation on Outcome in Takotsubo Syndrome: Data From the International Takotsubo Registry	International
Stiermaier T. (2017)	Prevalence and prognostic relevance of atrial fibrillation in patients with Takotsubo syndrome	International
Jesel L. (2018)	Atrial arrhythmias in Takotsubo cardiomyopathy: incidence, predictive factors, and prognosis	France

Author	Study Design	Multi-/Single-center	Outcome definition
Schneider B. (2018)	prospective, observational study	multicenter	-in-hospital mortality
Arcari L. (2020)	prospective, observational study	multicenter	- long-term mortality
Song B.G. (2010)	retrospective observational study	single-center	-long-term mortality
Dib C. (2008)	retrospective, partially prospective observational study	single-center	-in-hospital mortality
Azevedo P.M. (2018)	prospective, descriptive and correlational study	multicenter	-in-hospital mortality -all cause mortality
Martín-Demiguel I.(2019)	prospective, observational study	multicenter	-all cause death
El-Battrawy I.(2016)	retrospective , observational study	single-center	-in-hospital mortality -long-term mortality -cardiovascular mortality:
El-Battrawy I.(2021)	retrospective registry	multicenter	-long- term mortality
Stiermaier T. (2017)	prospective, cohort study	multicenter	-long- term mortality
Jesel L. (2018)	retrospective, cohort study	single center	-in-hospital mortality - cardiovascular death

Table 2. Risk of bias summary for the included studies

Hospital length of stay (days), mean ± SD	9±12	18±19
Cardiopulmonary resuscitation, n(%)	NA	NA
IABP (Intra-aortic balloon pump), n(%)	13 (8)	9 (17)
Cardiogenic shock, n(%)	18 (11)	14 (26)
QTc on admission (ms)	464±45	457±46
Heart rate (bpm.)	87±22	97±25
LVEF (%), mean ± SD	39±11	32±11
Chest pain on admission, n(%)	NA	NA
Stress factor: physical stress, n(%)	78 (48)	35 (66)
Stress factor: emotional stress, n(%)	24 (15)	4 (7.5)
Age (years)	68±12	70±12
Male, n(%)	2(16)	14 (26)
Patients with AF/AFL, n	X	53 (AF -35; AFL-10; AF and
Patients without AF/AFL, n	161	X
Subjects(n)	214	
Mean follow-up	700±656 days	
Title	Atrial arrhythmias in Takotsubo cardiomyopathy: incidence, predictive factors, and prognosis	
Author	Jesel L. (2018)	

Hospital length of stay (days), mean ± SD	6 (IR 4, 8)	8 (IR 4, 13)	6 (3–10)	7 (4–13) N=79	4±4	7±12	NA	16±23	NA	NA
Cardiopulmonary resuscitation, n(%)	NA	NA	107 (7.3)	22 (19.8)	NA	NA	NA	NA	NA	NA
IABP (Intra-aortic balloon pump), n(%)	NA	NA	34 (2.3)	7 (6.3)	NA	NA	NA	NA	NA	NA
Cardiogenic shock, n(%)	20 (6.9)	22 (22.7)	127 (8.8)	22 (20)	15 (17.7)	7 (38.9)	NA	NA	NA	NA
QTc on admission (ms)	NA	NA	457.9±48.6	453.2±60.9 (N=81)	480±53	474±49	NA	NA	NA	NA
Heart rate (bpm.)	NA	NA	86.5±21.1	94.5±23.0 (N=96)	101±26	97±31	NA	NA	NA	NA
LVEF (%), mean ± SD	42 (IR 35, 49)	36 (31, 45-IR)	41.3±11.8	37.2±11.1 (Data obtained during	37±10	39±9	NA	33±13	41.7±10	37.4±9.8
Chest pain on admission, n(%)	NA	NA	1061 (76.8)	71 (63.4)	65 (69.9)	15 (71.4)	NA	NA	188 (88.8)	20 (76.9)
Stress factor: physical stress, n(%)	123 (42.4)	41 (42.3)	498 (33.8)	50 (44.6)	54 (58.1)	10 (47.6)	NA	5(28)	NA	NA
Stress factor: emotional stress, n(%)	79 (27.2)	16 (16.5)	430 (29.2)	25 (22.3)	25 (29.9)	5 (23.8)	NA	10(56)	NA	NA
Age (years)	72 (IR: 63, 78)	78±5	66.1±13.0	73.8±12.2	65+11	76±7	NA	79±8	67±12	73.3±10
Male, n(%)	28 (9.7)	12 (12.4)	138 (9.4)	17 (15.2)	16 (17.2)	3 (14.3)	NA	0 (0)	NA	NA
Patients with AF/AFL, n	X	97(preexi sting AF-69;	X	112 AF on admission; preexisting AF-	X	21, previously known AF: 13(61.9%);	X	18 7,3%	X	26; 9 (3.8%) patients-
Patients without AF/AFL, n	290	X	1472	X	93	X	228	X	214	X
Subjects(n)	387		1584		114		246		240	
Mean follow-up	2.9 years (IR 1.3, 4.9)		5 years		1529±1121 days		12 months		35.9 months(IR 10–56 months)	
Title	Prevalence and prognostic relevance of atrial fibrillation in patients with Takotsubo syndrome		Impact of Atrial Fibrillation on Outcome in Takotsubo Syndrome: Data From the International Takotsubo Registry		Impact of concomitant atrial fibrillation on the prognosis of Takotsubo cardiomyopathy		Prevalence and Significance of Interatrial Block in Takotsubo Syndrome (from the RETAKO Registry)		Prevalence and prognostic impact of atrial fibrillation in patients with Takotsubo cardiomyopathy	
Author	Stiermaier T. (2017)		El-Battrawy I.(2021)		El-Battrawy I.(2016)		Martín-Demiguel I.(2019)		Azevedo P.M. (2018)	

Hospital length of stay (days), mean ± SD	NA	NA	NA	NA	NA	NA	NA	NA
Cardiopulmonary resuscitation, n(%)	NA	2 (50)	NA	NA	NA	NA	6 (3)	2 (6)
IABP (Intra-aortic balloon pump), n(%)	NA	NA	NA	NA	NA	NA	2 (1)	0 (0)
Cardiogenic shock, n(%)	NA	NA	NA	NA	NA	NA	9 (5)	5 (16)
QTc on admission (ms)	433.7± 25.4	NA	NA	NA	NA	NA	471±56	467±47
Heart rate (bpm.)	86.5±21	NA	NA	NA	NA	NA	87±24	90±20
LVEF (%), mean ± SD	NA	4 patients: 20-25%; 42%; 25-30%; 56%	NA	NA	NA	NA	52±15 (ventriculography)	45±14 (ventriculography)
Chest pain on admission, n(%)	NA	2 (50)	NA	NA	NA	NA	126 (71)	19 (59)
Stress factor: physical stress, n(%)	NA	NA	NA	NA	NA	NA	63 (36)	13 (40)
Stress factor: emotional stress, n(%)	NA	NA	NA	NA	NA	NA	66 (37)	8 (25)
Age (years)	68.2 ±12	4 patients: 68; 74; 70; 75	NA	NA	NA	NA	68±12	74±10
Male, n(%)	0 (0)	0 (0)	NA	NA	NA	NA	17 (10)	3 (9)
Patients with AF/AFL, n	X	4 (1 patient newly diagnosed; 3 patients-prior AF/MAT) 11,4%	X	6 6,9%	X	124 newly diagnosed AF 11,6%	X	32 newly diagnosed AF 15,3%
Patients without AF/AFL, n	31	X	81	X	947	X	177	X
Subjects(n)	**35**		87		1071		209	
Mean follow-up	NA		42 months (IR 19-72)		576 days (IR 27,2)		20–41 months	
Title	Malignant Arrhythmia in Apical Ballooning Syndrome: Risk Factors and Outcomes		Clinical characteristic, ballooning pattern, and long-term prognosis of transient left ventricular ballooning syndrome		Incidence, determinants and prognostic relevance of dyspnea at admission in patients with Takotsubo syndrome: results from the international multicenter GEIST registry		Ventricular Tachycardia and Atrial Fibrillation Complicating the Clinical Course of Tako-tsubo Cardiomyopathy: Results of the German Tako-tsubo Registry	
Author	Dib C. (2008)		Song B.G. (2010)		Arcari L. (2020)		Schneider B. (2018)	

Discussion

AF with other supraventricular tachyarrhythmias in patients with TTs are associated with unfavorable short and long-term prognosis. To our knowledge, this is the biggest analysis of incidence of the supraventricular tachyarrhythmias in this rare cardiovascular entity. Results of our study were concordant with the conclusions presented by Prasitlumkum et al. (5) in their article, although our insight into this topic was somewhat deeper and wider. Our literature search strategy was not restrained to the PubMed and EMBASE databases, but also Cochrane Central Register of Controlled Trials was screened for potentially eligible studies. What is more, we decided not to restrict our search to English language publications (we identified only 1 non-English language publication, which finally occurred not to be eligible). In our study we presented influence of supraventricular arrhythmias on short- and long-term outcome, unlike Prasitlumkum et al. whose study focused only on AF (5). Besides that, we demonstrated not only disadvantageous influence of atrial arrhythmias on all-cause mortality, long-term mortality but also intrahospital mortality.

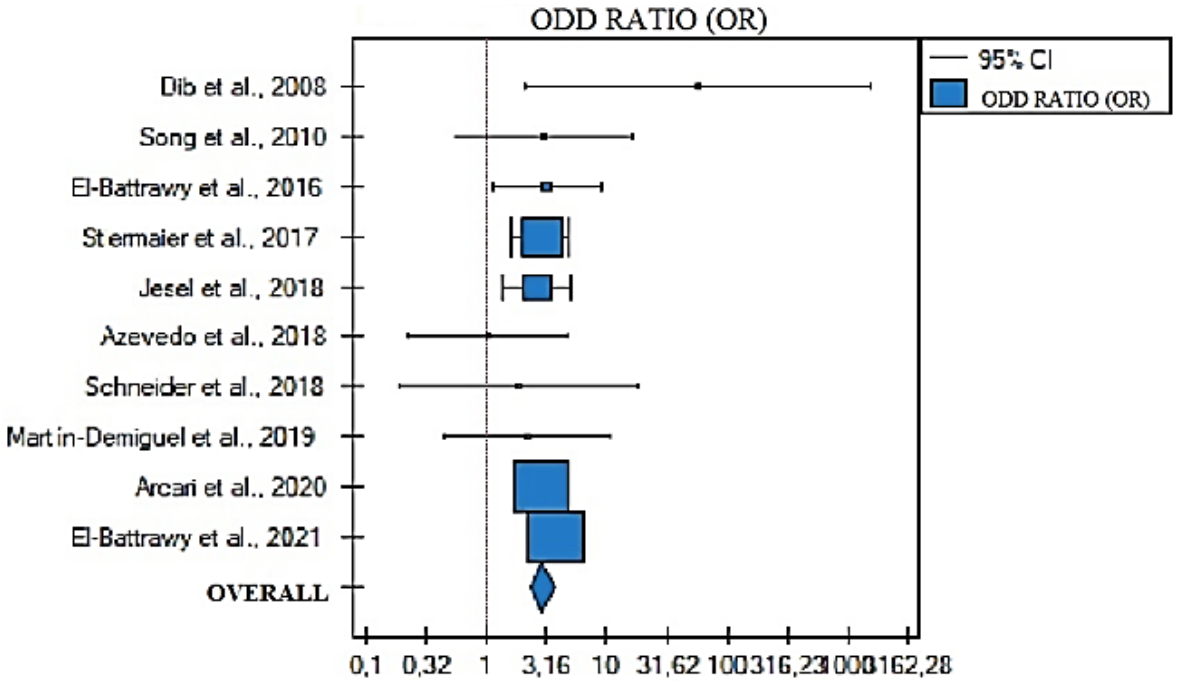

Figure 2. Forrest plot illustrating odd ratio (OR) with 95% confidence interval (CI) of all-cause death

Finally, our study comprised 10 publications with over 4 thousand participants, which was much more in comparison with cohort gathered by Prasitlumkum et al. (5). TTs is thought to comprise about 2% of all patients primarily admitted to the hospital with suspicion of ACS (20). The actual factors responsible for broken heart syndrome are not well established. Most cases are provoked by significant physical or/and mental disturbance. What is worth mentioning tako-tsubo episode may be triggered by situations with solely positive or negative influence (21). Our study revealed that atrial arrhythmias are associated with adverse short- and long-term outcomes. According to SWEDEHEART Registry patients with TTs had lower 30-day mortality rate in comparison with ST-elevation myocardial infarction (STEMI) patients, but higher than non-ST-elevation myocardial infarction (NSTEMI) patients. Long-term mortality prognosis was similar in TTs, NSTEMI and STEMI patients (22). In Canadian, population-based study, researchers demonstrated that patients with non-valvular AF (NVAF) and ACS had a 14% increased risk of death, hospitalization due to myocardial infarction (MI) and stroke in long-term follow-up, in comparison with ACS patients without NVAF (23). Konttila et al. in their TACOS study presented those patients with ACS and concomitant AF/AFl had significantly worse long-term outcome with higher all-cause mortality in comparison with patients in sinus rhythm (SR) (24). AF occurence was associated with a twofold magnified risk of composite endpoints (readmissions due to cardiac conditions, ischemic stroke or systemic embolism and all-cause death) mainly driven by cardiac readmission, in cohort with dual chamber pacemaker in small Chinese

trial (25). There is also group of evidence indicating that AF may act as a poor prognostic factor in cohort with dilated cardiomyopathy (DCM) (26). What is more, according to the recently published large cohort study, development of the AF in heart failure (HF) patients elevated risk of hospitalization due to acute heart failure, hemorrhagic stroke, faster renal function reduction, and all-cause mortality (27).

Pelliccia et al. in their publication identified 3 factors significantly associated with long-term mortality in TTs patients- advanced age, somatic stressors, and atypical ballooning pattern (28). Stiermaier et al. also investigated this topic and found male sex, cardiogenic shock/severe heart failure and presence of diabetes mellitus to be predictive factors for higher mortality in TTs patients (29). According to Pant et al., cardiac arrhythmias complicated about 26% of all TTs cases. The most common was AF, comprising 6.9%, then ventricular tachycardia (VT)- 3.2% and on the third place AFl-1,9%. What is noteworthy, almost 2% of patients experienced sudden cardiac arrest (SCA), what made it impossible to differentiate the exact arrhythmic mechanism of death (30). According to retrospective analysis of cardiac arrhythmias in TTs patients presented by Malanchini et al. atrial arrhythmias complicated hospitalization of almost 10%, and the most prevalent was atrial fibrillation (31). The same group of scientists concluded that atrial arrhythmias were predictors of increased mortality in univariate analysis but not in multivariate (31).

There are multiple theories explaining atrial arrhythmias occurrence in patients with TTs. Stiermaier et al. confirmed, that during acute/subacute phase of TTs, left atrium (LA) function measured by total LA-ejection fraction (LA-EF) significantly reduced in comparison with anterior-STEMI patients (32). LA dysfunction may be secondary to the LV function impairment. Due to wall motion abnormalities LV is unable to sustain normal stroke volume (SV), this leads to volume and then pressure LV overload. All of these increase LV diastolic filling pressure and cause secondary LA performance impairment. What supports this theory is the fact that, in the aforementioned study passive LA-EF (demonstrating LA function as a conduit) was severely impaired, however active LA-EF (demonstrating LA contraction), which should intercept compensatory function, has barely changed. This compensatory reaction during active phase of LA performance was noted by Ahtarovski et al. (33). Another mechanism responsible for increased LV filling pressure is associated with basal segments hyperkinesis, what may facilitate systolic anterior motion (SAM) phenomenon and dynamic left ventricular outflow tract obstruction (LVOTO). Increased sympathetic activation, excessive surge of catecholamines and neuropeptides with concomitant imbalance between sympathetic and parasympathetic cardiac nervous system are thought to have a major role in atrial fibrillation (34, 35). Japanese researchers performed endomyocardial biopsies in patients with TTs, in which, they found contraction-band necrosis and mononuclear cell infiltration, presence of which have been associated with catecholamine excess (36). It is thought that excessive β-adrenergic receptors stimulation results in intracellular calcium household disturbance (37). Although endomyocardial biopsies were performed within ventricles, we cannot exclude that similar process is ongoing within atria. Last but not least, there is growing group of evidence pointing towards inflammation as a key driver. Systemic inflammation is known to be connected with an elevated risk of atrial fibrillation as well as its reappearance (37-40).

Morel et al. reported an elevated level of C reactive protein (CRP) in patients with TTs. What is more, the level of CRP was related to the LVEF reduction and BNP release, besides that noradrenaline concentration and leukocytosis were also in relations in TTs patients (41). Results of the study conducted by Santoro et al. showed that, systemic inflammation plays a key role in TTs episode and specific inflammatory markers (interleukin 6 and 10) potentially may predict increased risk for an adverse outcome in follow-up (42). Previously the same group of researchers presented a case of 78-years old male with an acute TTs episode following influenza vaccination (43), what might support inflammatory mechanism of TTs. Essential for our analysis is observation that in every eligible trial, AF or other supraventricular arrhythmia affected population more advanced in age, what is concordant with worldwide epidemiologic trend (44, 45). Although in female gender age seems to play less important role in comparison with men (45), we are not able to preclude age differences in our overwhelmingly female cohort, biased final outcomes. Finally, we cannot exclude that all of the abovementioned mechanism and theories overlap each other and etiology of atrial arrhythmias in TTs has multifactorial background.

Observational nature of all studies needs to be recognized as a limitation, due to impossibility to exclude residual confounders. Undoubtedly different definitions of TTs emerge as one of the limitations of our study. In 6 studies (12-16, 18) a broken heart syndrome diagnosis was based on Mayo Tako-Tsubo diagnostic criteria, Jesel et al. (10) on the other hand used Madria's criteria, in Arcaris' publication Heart Failure Association Diagnostic criteria were taken into account (11), Song and Schneider used its

own inclusion and exclusion criteria (17, 19). Although we tried to acquire a completely homogenous research group, it was impossible- in trials led by Stiermaier, El-Batrrawy (2016), El-Batrrawy (2021), Azavedo and Dieb studied groups consisted of both: patients with supraventricular tachyarrhythmias present on admission/complicating hospitalization as well as patients with aforementioned tachyarrhythmias that had been diagnosed prior to the index hospitalization.

Noteworthy is that eligible trials were heterogeneous in relations to patients age, risk factors and follow-up duration what might affect final results of our study. Supraventricular tachyarrhythmias in eligible studies mainly consisted of AF, much fewer AFl (18) patients from Jesel et al. study) and only 1 multifocal atrial tachycardia (MAT), which is why in title of our study is restrained to AF. Atrial arrhythmias are associated with an increased risk for short- and long-term adverse outcomes in patients with TTs. Patients with supraventricular tachyarrhythmias during an acute episode of TTs should be more precisely monitored not only during hospitalization but also in the follow-up period in to reduce mortality.

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