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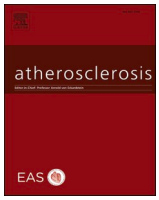

Statin therapy and outcome in Takotsubo syndrome patients: Results from the multicenter international GEIST registry

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ABSTRACT

Background and aims: Several studies have shown that endothelial dysfunction plays a role in the pathogenesis of Takotsubo syndrome (TTS). Given the potential benefit of statin therapy on endothelial dysfunction, we hypothesized that such treatment could improve outcome. Aim of our study was to evaluate clinical characteristics and outcome of TTS patients treated with statin therapy.

Methods: Patients were enrolled in the international multicenter GEIST (GErman Italian Spanish Takotsubo) registry. Demographic data, clinical features and drug therapy at discharge were recorded. Primary study outcome was the occurrence of all-cause death at follow-up.

Results: Study population included 2429 consecutive TTS patients: 1293 (53.2%) discharged on statin and 1136 (46.8%) without statin.

Patients with statin were older (age 72 ± 11 *vs* 69 ± 13 years, $p < 0.001$), with higher prevalence of hypertension (74.3% *vs* 60.3%, $p < 0.001$), diabetes (21.1% *vs* 14.7%, $p < 0.001$), dyslipidemia (56.1% *vs* 23.3%, $p < 0.001$), history of coronary artery disease (13.3% *vs* 6.3%, $p < 0.001$) and lower rates of in-hospital complications (14.7% *vs* 19.3%, $p = 0.003$). Survival analysis showed similar mortality rates between groups (log rank $p = 0.803$).

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At univariable analysis, statin therapy at discharge was not associated with lower mortality (HR: 0.97, 95% CI 0.74–1.26, $p = 0.803$). At multivariable analysis age (HR: 1.06 95% CI 1.04–1.08, $p < 0.001$), male sex (HR: 1.83, 95% CI 1.20–2.80, $p = 0.005$), diabetes (HR: 2.55, 95% CI 1.83–3.54 $p < 0.001$), malignancies (HR: 2.41, 95% CI 1.68–3.44, $p < 0.001$) and physical trigger (HR: 2.24, 95% CI 1.62–3.10, $p < 0.001$) were associated with increased mortality.

Conclusions: Statin therapy after a TTS event was not associated with better prognosis at follow-up.

1. Introduction

Takotsubo syndrome (TTS) is a reversible acute left ventricular systolic dysfunction, which resembles an acute coronary syndrome but in absence of a "culprit lesion" in the coronary arteries. It is frequently triggered by an acute stress, either emotional or physical [1].

Several theories have tried to explain the pathophysiology of TTS. Catecholamines seem to have a central role, although other factors (i.e., oxidative stress, estrogen shortage, transitory coronary artery spasm, genetic susceptibility, and infectious agents) may also be involved [2,3].

The hyperactivation of the sympathetic system leads to myocardial stunning through a hyperdynamic contractility of cardiomyocytes, a microvascular dysfunction, or an epicardial vasospasm [2].

Different studies have demonstrated that oxidative stress and catecholaminergic excessive production strongly regulate arterial vasomotion and adversely affect endothelial function [4,5].

Therefore, biochemical mechanisms leading to TTS can negatively influence endothelial function.

As well known, statins have pleiotropic effects apart from serum lipid-lowering effect. One of the major target organs for the effects of statins is the vascular endothelium. Many recent studies have shown that vascular effects of statins appear to involve restoration or improvment of endothelial function by increasing nitric oxide production, promoting re-reendothelialization, after arterial injury, and inhibiting inflammatory responses [6–10].

The concept of direct pleiotropic effects of statins on vascular endothelial function in humans has also been demonstrated by comparing the effects of different lipid-lowering strategies. Statin therapy significantly and markedly improved flow mediated dilation (FMD) of the brachial artery compared with other lipid-lowering therapies, despite the similar reduction of low-density lipoprotein (LDL) [11–13].

Given the favorable effects of statins on endothelial dysfunction and its possible role in the pathogenesis of TTS, in this study we aimed to investigate whether statin treatment may improve the long-term clinical outcome in patients with TTS.

2. Patients and methods

This is a multicenter observational study with the aim of evaluating the influence of statin therapy on the outcome of patients with previous hospitalization for TTS. The study includes patients with TTS diagnosis prospectively enrolled in the German Italian Spanish Takotsubo (GEIST) Registry. TTS was diagnosed according to the Heart Failure Association Criteria [2]. Inclusion and exclusion criteria have been previously reported (ClinicalTrials.gov Identifier: NCT04361994) [14]. Data on the clinical profile (demographic characteristics, clinical presentation, laboratory tests, electrocardiography/echocardiography parameters, therapy and medication), in-hospital course and complications, and short/long-term prognosis were gathered prospectively and retrospectively. All patients were managed in accordance to the Declaration of Helsinki and signed an informed consent in order to process their personal data for scientific research purpose. The registry has been approved by the Ethics Committee of each institution.

In total, 2813 patients with TTS were enrolled in the GEIST registry; of these 384 were excluded from the study due to in-hospital death (n = 83) or missing information on pharmacological therapy at discharge (n = 297). The remaining 2429 patients were divided into two groups based on prescription of statin upon hospital discharge (Fig. 1).

The follow-up was performed by outpatient clinic visits and structured telephone interviews. The occurrence of prespecified adverse clinical events was documented. Research outcome measures were evaluated during the longest available follow-up period.

The primary study outcome is the occurrence of all-cause death.

2.1. Statistical analysis

To compare categorical variables, Chi-square analysis or Fisher exact-test were utilized. Continuous variables were expressed as mean SD or median with interquartile range (IQR). To compare continuous variables, Student's t-test for independent samples or Mann-Whitney *U* test was employed.

Univariable and multivariable logistic regression analysis was performed to calculate estimated Odds Ratios (OR) and 95% confidence intervals (CI) for factors associated with prescription of statin at hospital discharge, while univariable and multivariable Cox regression analyses were performed to assess factors independently associated with long-term mortality in the overall cohort. Kaplan-Meier curves and log-rank test were used to assess survival function at follow-up. All data were analyzed with SPSS software version 25.0 (SPSS Inc).

3. Results

3.1. Study population

Consecutive TTS patients (n = 2429) discharged alive were enrolled; 1293 (53.2%) patients were discharged on statin therapy. Among these, 56.1% (n = 709) were already receiving statin therapy, while the remaining 43.9% (n = 584) initiated therapy upon admission. Baseline demographic and clinical characteristics within the two cohorts stratified by statin prescription at discharge are reported in Table 1.

Patients receiving statin therapy were older (age 72 ± 11 *vs* 69 ± 13 years, $p < 0.001$), with higher prevalence of hypertension (74.3% *vs* 60.3%, $p < 0.001$), diabetes (21.1% *vs* 14.7%, $p < 0.001$), dyslipidemia (56.1% vs 23.3%, $p < 0.001$) and history of coronary artery disease (13.3% *vs* 6.3%, $p < 0.001$) (Fig. 2).

Patients with statin therapy at discharge were more likely to have been admitted with a clinical presentation of chest pain (63.6% *vs* 54.8%, $p < 0.001$), following an emotional triggered TTS (39.7% *vs* 33.2%, $p = 0.01$) and having higher prevalence of apical ballooning at the admission echocardiogram (87.5% *vs* 82.5%, $p = 0.001$) with lower rates of in-hospital complications (14.7% *vs* 19.3%, $p = 0.003$), including cardiogenic shock (5.3% *vs* 9.5%, $p < 0.001$), catecholamine administration (6.1% *vs* 10.9%, $p < 0.001$) and necessity of orotracheal intubation (OTI – 4.8% *vs* 7.8%, $p = 0.003$).

At multivariable analysis, the following factors were independently associated with prescription of statin: higher age (OR: 1.01, 95% CI (1.00–1.02)], $p = 0.014$), male sex (OR: 1.51, 95 % CI (1.12.-2.02)], $p = 0.006$), hypertension (OR: 1.36, 95% CI (1.11–1.66)], $p = 0.003$), dyslipidemia (OR: 3.36, 95% CI (2.79–4.05)], $p < 0.001$), diabetes (OR: 1.42, 95% CI (1.12–1.81)], $p = 0.004$), physical trigger (OR: 0.65, 95% CI (0.53–0.78)], $p < 0.001$), and lower rates of in-hospital complications (OR: 0.69, 95% CI (0.53–0.87)], $p = 0.002$) (Table 2).

3.2. Outcome data

The median follow-up time was 386 days (39–1427) for patients with statin therapy and 372 days (50–1434) for those without this treatment ($p = 0.778$).

During follow-up, the incidence of the primary outcome (all-cause death) was 9.1% in patients on statin *vs* 9.2% in patients without statin therapy. The Kaplan-Meier analysis showed similar mortality rate between statin treated *vs* untreated patients (log rank $p = 0.803$) (Fig. 3).

At univariable analysis, there was no significant association between statin and the risk of mortality (HR: 0.97, 95% CI 0.74–1.26, $p = 0.803$).

At multivariable analysis, variables associated with increased mortality rates were: higher age (HR: 1.06 95% CI 1.04–1.08, $p < 0.001$), male sex (HR: 1.83, 95% CI 1.20–2.80, $p = 0.005$), diabetes (HR: 2.55, 95% CI 1.83–3.54 $p < 0.001$), pulmonary disease (HR: 1.55, 95% CI 1.05–2.28 $p = 0.027$), malignancies (HR: 2.41, 95% CI 1.68–3.44, $p < 0.001$), physical trigger (HR: 2.24, 95% CI 1.62–3.10, $p < 0.001$), lower LVEF (0.97, 95% CI 0.96–0.99, $p < 0.001$), occurrence of in-hospital complications (HR: 1.78, 95% CI 1.24–2.56, $p = 0.002$) and lack of RAS-inhibitor therapy (HR: 0.60, 95% CI 0.43–0.84, $p = 0.003$) (Table 3).

4. Discussion

We report one of the first studies investigating clinical features and long-term outcomes of TTS patients who were discharged on statins or not through a large multicenter European registry.

The main findings of this real-world registry can be summarized as follows:

1 about half of the patients were discharged with statin and this prescription was more common in patients with higher cardiovascular risk profile;
2 prescription of statins at discharge was associated with older age, multiple CV risk factor,s and lower in-hospital complications;
3 statin therapy was not associated with lower mortality at follow-up (Fig. 4).

Endothelial dysfunction plays a role in the pathogenesis of TTS [15,16] and treatment with statins could improve endothelial function and reduce the risk of adverse cardiovascular events at long-term follow up [7,8].

Many investigations were conducted to illustrate the relationship between endothelial function and TTS.

Two groups investigated the relationship between vaso-motility, which is directly connected to endothelial function, and TTS via brachial artery flow-mediated dilation (FMD).

Vasilieva et al. investigated FMD in patients with TTS, with ST-elevation acute myocardial infarction (STEMI) and in healthy volunteers. FMD levels were substantially lower in TTS patients during the acute period than in STEMI patients and in healthy volunteers ($p < 0.01$). After 1–3 weeks, the FMD test results of TTS patients had considerably improved, and no significant differences were identified between these findings and those of STEMI patients [15].

Carbonara et al. analyzed the variability of FMD in a group of TTS patients during the course of their hospital stay. The results demonstrated a severe reduction of FMD, measured in the acute phase of TTS, and its subsequent recovery [17].

Martin et al. measured reactive hyperemia, as parameter of endothelial function and vascular responses to acute mental stress, using peripheral arterial tonometry (PAT) at baseline and following 3 acute mental stress tests in female patients with TTS. In individuals who had previously experienced TTS, there was enhanced vascular reactivity and reduced endothelial function in response to acute mental stress compared with age-matched post-menopausal controls and patients with myocardial infarction (MI) [16].

In another study, Patel et al. evaluated coronary vascular reactivity of patients who were previously diagnosed with TTS by coronary epicardial and microvascular responses to intracoronary acetylcholine (ACH) and to nitroglycerin**.** The study demonstrated impaired responses to ACH with preserved epicardial responses to nitroglycerin, suggesting the presence of endothelial dysfunction in TTS [18].

Medications generally used for myocardial infarction treatment (beta-blockers, ACE-inhibitors, angiotensin receptor blockers) have been demonstrated to positively influence endothelial function [19–25] and some observational registries showed that they could improve TTS outcomes [26–29]. However, no studies explored the potential benefit of statin therapy so far.

In the present study, we did not find any potential benefit in terms of survival among patients treated with statins. Statin therapy was more likely prescribed in older patients with dyslipidemia or other cardiovascular risk factors, in accordance to the clinical indications and current guidelines on prevention, regardless of TTS diagnosis.

On the other hand, having a physical trigger was associated with a reduced prescription rate for the statin.

The results of our study, showing that a statin treatment does not

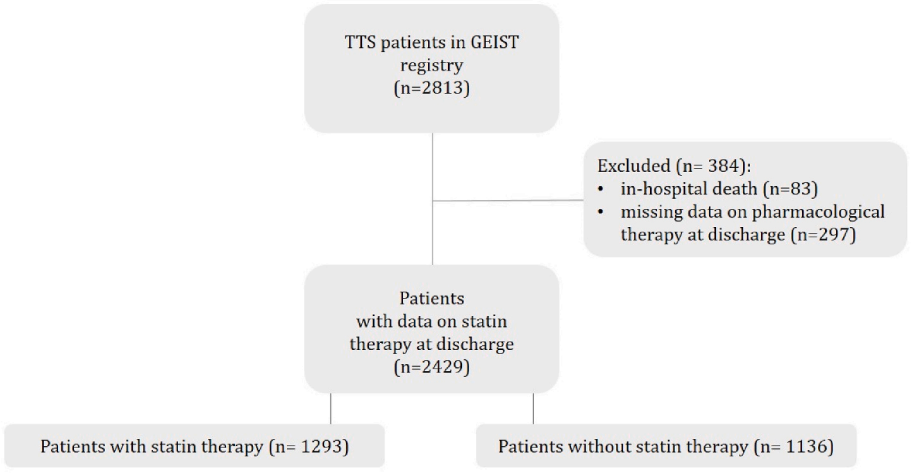

Fig. 1. Study design diagram.
Comparison between TTS patients discharged with and without statins. GEIST = German Italian Spanish Takotsubo; TTS = Takotsubo syndrome.

Table 1
Baseline characteristics of patients within the overall and matched cohort.

Variable	No statin therapy (n = 1136)	Statin therapy (n = 1293)	p
Age (years)	69 ± 13	72 ± 11	**<0.001**
Male sex (%)	118/1136 (10.4)	159/1293 (12.3)	0.140
Comorbidities			
Hypertension (%)	684/1135 (60.3)	960/1292 (74.3)	**<0.001**
Diabetes mellitus (%)	167/1133 (14.7)	272/1291 (21.1)	**<0.001**
Dyslipidemia (%)	236/1014 (23.3)	709/1264 (56.1)	**<0.001**
Current Smoker (%)	200/1132 (17.7)	227/1292 (17.6)	0.950
Pulmonary disease (%)	149/994 (15.0)	173/1160 (14.9)	0.961
Malignancies (%)	156/957 (16.3)	159/1132 (14.9)	0.151
Coronary artery disease (%)	67/1062 (6.3)	160/1206 (13.3)	**<0.001**
Clinical presentation			
Chest pain (%)	599/1092 (54.8)	779/1224 (63.6)	**<0.001**
Dyspnea (%)	411/1091 (37.7)	410/1226 (33.4)	0.034
Stressful trigger (%)	767/1079 (71.1)	851/1229 (69.2)	0.335
Emotional (%)	370/1114 (33.2)	503/1267 (39.7)	**0.001**
Physical (%)	434/1131 (38.4)	382/1292 (29.6)	**<0.001**
ECG findings			
Atrial fibrillation (%)	153/1003 (15.2)	171/1138 (15.0)	0.883
ST-changes (%)	746/925 (80.6)	902/1166 (77.4)	0.067
Echocardiographic findings			
LVEF (%)	38.67 ± 13.03	38.95 ± 13.51	0.620
Apical ballooning (%)	926/1123 (82.5)	1123/1284 (87.5)	0.001
Mid-ventricular ballooning (%)	166/1115 (14.9)	141/1282 (11.0)	0.004
Basal ballooning (%)	33/1112 (3.0)	17/1280 (1.3)	0.005
Focal (%)	4/1013 (0.4)	4/1131 (0.4)	0.876
In-hospital course			
In-hospital complications (%)	212/1100 (19.3)	187/1272 (14.7)	**0.003**
Pulmonary rdema (%)	88/1116 (7.9)	102/1269 (8.0)	0.891
Cardiogenic shock (%)	107/1132 (9.5)	68/1293 (5.3)	**<0.001**
Arrhythmias (%)	77/723 (10.7)	68/728 (9.3)	0.406
Catecholamine administration (%)	121/1110 (10.9)	73/1207 (6.1)	**<0.001**
OTI (%)	80/1027 (7.8)	60/1249 (4.8)	**0.003**
In-hospital stay (days)	9.56 ± 10.73	8.36 ± 7.70	0.002
Discharge therapy			
Aspirin (%)	460/1134 (40.5)	938/1279 (73.3)	<0.001
DAPT (%)	60/837 (7.2)	132/840 (15.7)	<0.001
Anticoagulant (%)	181/1074 (16.9)	225/1120 (20.1)	0.051
Beta-blockers (%)	709/1085 (65.4)	972/1224 (79.4)	<0.001
ACEi/ARB (%)	679/1135 (59.8)	978/1288 (75.9)	<0.001
Follow up (days)	372 (50, 1434)	386 (39, 1427)	0.778
Mortality (%)	101/1097 (9.2)	115/1267 (9.1)	0.913

Data are presented as no. (%), mean ± standard deviation, median (interquartile range). Takotsubo syndrome (TTS), left ventricular ejection fraction (LVEF), orotracheal intubation (OTI), dual antiplatelet therapy (DAPT).

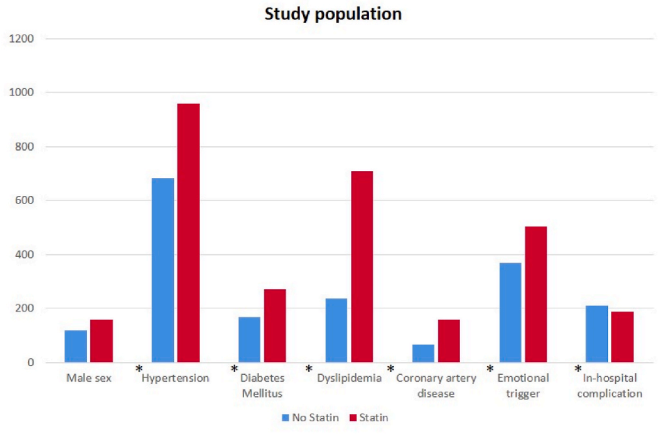

Fig. 2. Study population.
Prevalence of comorbidities, type of trigger and in-hospital complications among patients with Takotsubo syndrome discharged with and without statin. * Statistical differences of clinical features ($p < 0.05$).

affect survival at a median 1 year follow up, support the hypothesis that TTS is an acute heart failure syndrome and not a form of acute coronary syndrome, therefore it could be speculated that a long-term heart failure treatment could be preferred.

Given the lower rate of in-hospital complications in patients discharged with statins, it cannot be excluded that statins therapy, due to their favorable effect on endothelial function, may have a beneficial role during the acute phase of TTS [17]. Even if it is reasonable that statin therapy was started at patient's admission, as the patients were initially treated for acute coronary syndrome, this hypothesis cannot be confirmed since in this registry, data on drug therapy and dosages before and during hospital stay were not routinely collected. Therefore, randomized controlled trials are needed to evaluate the possible role of statin treatment during the acute phase on reducing the rate of in-hospital complications.

4.1. Limitations

Details on medication treatment prior to TTS admission were not systematically evaluated. At follow-up, drug dose, adherence to therapy, and changes in treatment regimen were not regularly examined.

Since data on cardiovascular and non-cardiovascular mortality were not gathered prospectively, the primary outcome was all-cause death.

The reported data is derived from registry records and may be

Table 2
Univariable and multivariable analysis for factors associated with statin-therapy at discharge.

Factors associated with statin therapy at discharge				
Variable	Univariable		Multivariable	
	OR (95 % CI)	*p*	OR (95 % CI)	*p*
Age	1.019 (1.012–1.026)	<0.001	1.010 (1.002–1.018)	0.014
Male sex	1.210 (0.939–1.557)	0.140	1.508 (1.124–2.023)	0.006
Hypertension	1.907 (1.605–2.265)	<0.001	1.358 (1.111–1.660)	0.003
Dyslipidemia	3.648 (3.050–4.363)	<0.001	3.361 (2.792–4.046)	<0.001
Diabetes	1.544 (1.249–1.908)	<0.001	1.423 (1.117–1.814)	0.004
Current smoking	0.993 (0.806–1.225)	0.950	–	–
Pulmonary disease	0.994 (0.784–1.261)	0.961	–	–
Malignancies	0.839 (0.660–1.066)	0.152	–	–
Physical trigger	0.674 (0.569–0.798)	<0.001	0.646 (0.533–0.783)	<0.001
LVEF	1.002 (0.995–1.008)	0.620	–	–
Apical ballooning	1.484 (1.184–1.860)	0.001	NS	NS
In-hospital complications	0.722 (0.582–0.896)	0.003	0.681 (0.534–0.868)	0.002

Left ventricular ejection fraction (LVEF), non-significant (NS).

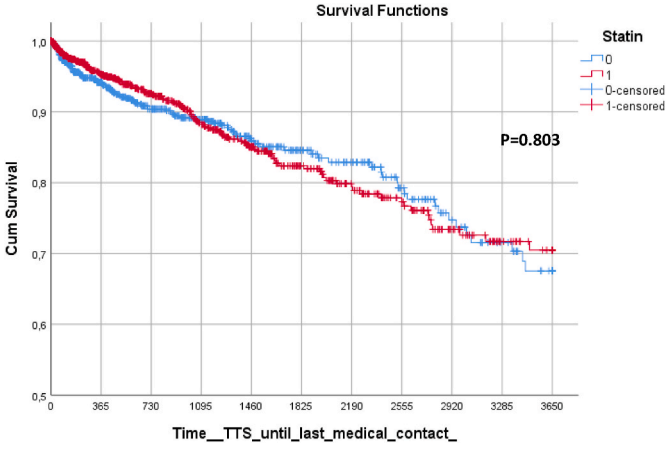

Fig. 3. Kaplan-Meier survival curves for long-term mortality among TTS patients discharged with statin.

influenced by residual confounding factors that extend beyond those examined. The precise role of endothelial dysfunction in Takotsubo syndrome (TTS) remains incompletely understood in the current literature and is beyond the objective of the present study.

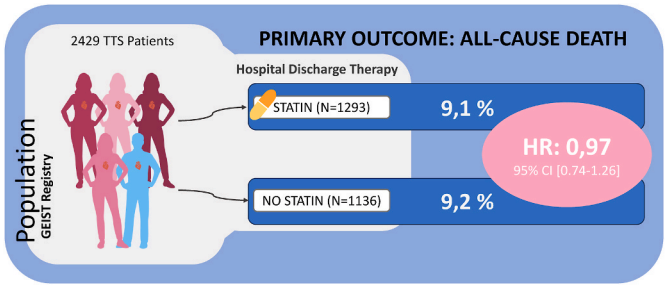

Fig. 4. Graphical abstract.
Statin therapy and outcome in Takotsubo syndrome. Overview of the methods and the conclusions of the study. TTS: Takotsubo syndrome; GEIST: GErman Italian Spanish Takotsubo; HR: Hazard ratio; CI: Confidence interval.

4.2. Conclusion

Our study proved for the first time in a large real-world population that statin medication may not reduce mortality in TTS patients. This result reinforces the hypothesis that TTS is a heart failure syndrome ("catecholamine induced") more than an acute coronary syndrome, therefore treatment of heart failure in the long term could be more effective. Further research is needed to confirm this hypothesis and to

Table 3
Univariable and multivariable Cox regression analysis for factors associated with long-term mortality.

Long-term mortality				
Variable	Univariable		Multivariable	
	HR (95% CI)	*p*	HR (95% CI)	*p*
Age	1.068 (1.052–1.084)	<0.001	1.063 (1.044–1.082)	<0.001
Male sex	1.899 (1.316–2.742)	0.001	1.831 (1.199–2.796)	0.005
Hypertension	1.393 (1.016–1.908)	0.039	NS	NS
Dyslipidemia	1.045 (0.786–1.390)	0.760	–	–
Diabetes	2.445 (1.838–3.251)	<0.001	2.547 (1.833–3.539)	<0.001
Current smoking	0.755 (0.521–1.094)	0.137	–	–
Pulmonary disease	1.893 (1.323–2.710)	<0.001	1.549 (1.052–2.280)	0.027
Malignancies	2.758 (2.007–3.789)	<0.001	2.407 (1.682–3.444)	<0.001
Physical trigger	2.480 (1.891–3.253)	<0.001	2.241 (1.620–3.099)	<0.001
LVEF (%)	0.963 (0.952–0.975)	<0.001	0.971 (0.956–0.985)	<0.001
Apical ballooning	1.336 (0908–1.966)	0.141	–	–
In-hospital complications	2.903 (2.164–3.895)	<0.001	1.779 (1.237–2.559)	0.002
RAS-inhibitor	0.634 (0.481–0.836)	0.001	0.604 (0.433–0.844)	0.003
BB	0.880 (0.653–1.185)	0.399	–	–
Statin therapy	0.966 (0.738–1.265)	0.803	–	–

Left ventricular ejection fraction (LVEF), non-significant (NS).

investigate the possible role of statin treatment during the acute phase.

CRediT authorship contribution statement

Giuseppina Novo: Conceptualization, of the paper, Methodology, Investigation, Data curation, Investigation, Writing – review & editing. **Luca Arcari:** Conceptualization, of the paper, Formal analysis, Investigation, Writing – review & editing. **Thomas Stiermaier:** Formal analysis, Investigation, Data curation, revision and editing of the manuscript. **Chiara Alaimo:** Formal analysis, Investigation, Data curation, Writing – review & editing, of the manuscript. **Ibrahim El-Battrawy:** extraction and, Formal analysis, of data, Investigation, Data curation, revision and, editing, of the manuscript. **Luca Cacciotti:** extraction and formal, Formal analysis, of data, Investigation, Data curation, revision and editing of the manuscript. **Federico Guerra:** extraction and, Formal analysis, of data, Investigation, Data curation, revision and editing of the manuscript. Maria. **Beatrice Musumeci:** extraction and, Formal analysis, of data, Investigation, Data curation, revision and editing of the manuscript. **Enrica Mariano:** extraction and, Formal analysis, of data, Investigation, Data curation, revision and editing of the manuscript. **Giuseppe Parisi:** extraction and, Formal analysis, of data, Investigation, Data curation, revision and editing of the manuscript. **Roberta Montisci:** extraction and, Formal analysis, of data, Investigation, Data curation, revision and editing of the manuscript. **Ravi Vazirani:** extraction and, Formal analysis, of data, Investigation, Data curation, revision and editing of the manuscript. **Alberto Perez Castellanos:** extraction and, Formal analysis, of data, Investigation, Data curation, revision and editing of the manuscript. **Aitor Uribarri:** extraction and, Formal analysis, of data, Investigation, Data curation, Investigation, Data curation, revision and editing of the manuscript. **Miguel Corbi-Pascual:** extraction and, Formal analysis, of data, Investigation, Data curation, revision and, editing, of the manuscript. **Jorge Salamanca:** extraction and, Formal analysis, of data; revision and, editing, of the manuscript. **Ibrahim Akin:** extraction and, Formal analysis, of data, Investigation, Data curation, revision and editing of the manuscript. **Holger Thiele:** extraction and, Formal analysis, of data, Investigation, Data curation, revision and editing of the manuscript. **Natale Daniele Brunetti:** extraction and, Formal analysis, of data, Investigation, Data curation, revision and editing of the manuscript, Supervision. **Ingo Eitel:** extraction and, Formal analysis, of data, Investigation, Data curation, revision and editing of the manuscript, Supervision. **Iván J. Núñez Gil:** extraction and, Formal analysis, of data, Investigation, Data curation, revision and editing of the manuscript, Supervision. **Francesco Santoro:** Conceptualization, of the paper, Methodology, Investigation, Data curation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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