

Impact of aspirin on takotsubo syndrome: a propensity score-based analysis of the InterTAK Registry

**Fabrizio D’Ascenzo^{1*}, Sebastiano Gili², Maurizio Bertaina¹, Mario Iannaccone¹,
 Victoria L. Cammann³, Davide Di Vece³, Ken Kato³, Andrea Saglietto¹,
 Konrad A. Szawan³, Antonio H. Frangieh^{4,5}, Beatrice Boffini²,
 Margherita Annaratone⁶, Annahita Sarcon⁷, Rena A. Levinson^{3,8}, Jennifer Franke⁹,
 L. Christian Napp¹⁰, Milosz Jaguszewski¹¹, Michel Noutsias¹², Thomas Münzel¹³,
 Maike Knorr¹³, Susanne Heiner¹³, Hugo A. Katus⁹, Christof Burgdorf¹⁴,
 Heribert Schunkert^{4,5}, Holger Thiele¹⁵, Johann Bauersachs¹⁰, Carsten Tschöpe¹⁶,
 Burkert M. Pieske¹⁶, Lawrence Rajan¹⁷, Guido Michels¹⁸, Roman Pfister¹⁸,
 Alessandro Cuneo¹⁹, Claudius Jacobshagen²⁰, Gerd Hasenfuß²⁰, Mahir Karakas^{21,22},
 Wolfgang Koenig^{4,5}, Wolfgang Rottbauer²³, Samir M. Said²⁴,
 Ruediger C. Braun-Dullaeus²⁴, Adrian Banning²⁵, Florim Cuculi²⁶, Richard Kobza²⁶,
 Thomas A. Fischer²⁷, Tuija Vasankari²⁸, K.E. Juhani Airaksinen²⁸,
 Grzegorz Opolski²⁹, Rafal Dworakowski³⁰, Philip MacCarthy³⁰, Christoph Kaiser³¹,
 Stefan Osswald³¹, Leonarda Galiuto³², Filippo Crea³², Wolfgang Dichtl³³,
 Wolfgang M. Franz³³, Klaus Empen^{34,35}, Stephan B. Felix^{34,35}, Clément Delmas³⁶,
 Olivier Lairez³⁶, Ibrahim El-Battrawy^{37,38}, Ibrahim Akin^{37,38}, Martin Borggrefe^{37,38},
 John D. Horowitz³⁹, Martin Kozel⁴⁰, Petr Tousek⁴⁰, Petr Widimský⁴⁰,
 Ekaterina Gilyarova⁴¹, Alexandra Shilova⁴¹, Mikhail Gilyarov⁴¹,
 Giuseppe Biondi-Zoccai⁴², David E. Winchester⁴³, Christian Ukena⁴⁴,
 Michael Neuhaus⁴⁵, Jeroen J. Bax⁴⁶, Abhiram Prasad⁴⁷, Carlo Di Mario⁴⁹,
 Michael Böhm⁴⁴, Mauro Gasparini⁶, Frank Ruschitzka³, Eduardo Bossone⁵⁰,
 Rodolfo Citro⁵¹, Mauro Rinaldi¹, Gaetano Maria De Ferrari⁴⁸, Thomas Lüscher^{52,53},
 Jelena R. Ghadri³, and Christian Templin³**

¹Division of Cardiology, Department of Medical Sciences, AOU Città della Salute e della Scienza, University of Turin, Turin, Italy; ²Centro Cardiologico Monzino, IRCCS, Milan, Italy; ³Department of Cardiology, University Heart Center, University Hospital Zurich, Zurich, Switzerland; ⁴Deutsches Herzzentrum München, Technische Universität München, Munich, Germany; ⁵DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany; ⁶Department of Mathematical Sciences, Politecnico di Torino, Turin, Italy; ⁷Section of Cardiac Electrophysiology, Department of Medicine, University of California-San Francisco, San Francisco, CA, USA; ⁸Division of Biological Sciences, University of California San Diego, San Diego, CA, USA; ⁹Department of Cardiology, Heidelberg University Hospital, Heidelberg, Germany; ¹⁰Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany; ¹¹First Department of Cardiology, Medical University of Gdansk, Gdansk, Poland; ¹²Department of Internal Medicine III, Division of Cardiology, Angiology and Intensive Medical Care, University Hospital Halle, Martin-Luther-University Halle, Halle, Germany; ¹³Center for Cardiology, Cardiology 1, University Medical Center Mainz, Mainz, Germany; ¹⁴Heart and Vascular Centre Bad Bevensen, Bad Bevensen, Germany; ¹⁵Department of Internal Medicine/Cardiology, Heart Center Leipzig – University Hospital, Leipzig, Germany; ¹⁶Department of Cardiology, Charité, Campus Rudolf Virchow, Berlin, Germany; ¹⁷TJ Health Partners Heart and Vascular, Glasgow, KY, USA; ¹⁸Department of Internal Medicine III, Heart Center University of Cologne, Cologne, Germany; ¹⁹Krankenhaus “Maria Hilf” Medizinische Klinik, Stadtlohn, Germany; ²⁰Clinic for Cardiology and Pneumology, Georg August University Goettingen, Goettingen, Germany;

*Corresponding author: Division of Cardiology, Department of Medical Sciences, AOU Città della Salute e della Scienza, University of Turin, Corso Bramante 88-90, 10126 Turin, Italy. Tel: +39 011 6334446, Email: fabrizio.dascenzo@gmail.com

²¹Department of General and Interventional Cardiology, University Heart Center Hamburg, Hamburg, Germany; ²²DZHK (German Centre for Cardiovascular Research), partner site Hamburg/Kiel/Luebeck, Hamburg, Germany; ²³Department of Internal Medicine II – Cardiology, University of Ulm, Medical Center, Ulm, Germany; ²⁴Internal Medicine/Cardiology, Angiology, and Pneumology, Magdeburg University, Magdeburg, Germany; ²⁵Department of Cardiology, John Radcliffe Hospital, Oxford University Hospitals, Oxford, UK; ²⁶Department of Cardiology, Kantonsspital Lucerne, Lucerne, Switzerland; ²⁷Department of Cardiology, Kantonsspital Winterthur, Winterthur, Switzerland; ²⁸Heart Center, Turku University Hospital and University of Turku, Turku, Finland; ²⁹Department of Cardiology, Medical University of Warsaw, Warsaw, Poland; ³⁰Department of Cardiology, Kings College Hospital, Kings Health Partners, London, UK; ³¹Department of Cardiology, University Hospital Basel, Basel, Switzerland; ³²Fondazione Policlinico Universitario A. Gemelli, IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy; ³³University Hospital for Internal Medicine III (Cardiology and Angiology), Medical University Innsbruck, Innsbruck, Austria; ³⁴Department of Internal Medicine B, University Medicine Greifswald, Greifswald, Germany; ³⁵DZHK (German Centre for Cardiovascular Research), partner site Greifswald, Greifswald, Germany; ³⁶Department of Cardiology and Cardiac Imaging Center, University Hospital of Rangueil, Toulouse, France; ³⁷First Department of Medicine, Faculty of Medicine, University Medical Centre Mannheim (UMM) University of Heidelberg, Mannheim, Germany; ³⁸DZHK (German Center for Cardiovascular Research), partner site, Heidelberg-Mannheim, Mannheim, Germany; ³⁹Department of Cardiology, Basil Hetzel Institute, Queen Elizabeth Hospital, University of Adelaide, Adelaide, Australia; ⁴⁰Cardiocenter, Third Faculty of Medicine, Charles University in Prague and University Hospital Královské Vinohrady, Prague, Czech Republic; ⁴¹Intensive Coronary Care Unit, Moscow City Hospital # 1 named after N. Pirogov, Moscow, Russia; ⁴²Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy; ⁴³Department of Medicine, College of Medicine, University of Florida, Gainesville, FL, USA; ⁴⁴Klinik für Innere Medizin III, Universitätsklinikum des Saarlandes, Homburg, Germany; ⁴⁵Department of Cardiology, Kantonsspital Frauenfeld, Frauenfeld, Switzerland; ⁴⁶Department of Cardiology, Leiden University Medical Centre, Leiden, The Netherlands; ⁴⁷Division of Cardiovascular Diseases Mayo Clinic, Rochester, MN, USA; ⁴⁸Department of Molecular Medicine University of Pavia, and Cardiac Intensive Care Unit and Laboratories for Experimental Cardiology, IRCCS Fondazione Policlinico San Matteo, Pavia, Italy; ⁴⁹Structural Interventional Cardiology, University Hospital Careggi, Florence, Italy; ⁵⁰Division of Cardiology, 'Antonio Cardarelli' Hospital, Naples, Italy; ⁵¹Heart Department, University Hospital 'San Giovanni di Dio e Ruggi d'Aragona', Salerno, Italy; ⁵²Center for Molecular Cardiology, Schlieren Campus, University of Zurich, Zurich, Switzerland and ⁵³Royal Brompton and Harefield Hospitals Trust and Imperial College, London, UK

Received 16 March 2018; revised 4 November 2019; accepted 7 November 2019; online publish-ahead-of-print 20 December 2019

Aims

The aim of the present study was to investigate the impact of aspirin on prognosis in takotsubo syndrome (TTS).

Methods and results

Patients from the International Takotsubo (InterTAK) Registry were categorized into two groups based on aspirin prescription at discharge. A comparison of clinical outcomes between groups was performed using an adjusted analysis with propensity score (PS) stratification; results from the unadjusted analysis were also reported to note the effect of the PS adjustment. Major adverse cardiac and cerebrovascular events (MACCE: a composite of death, myocardial infarction, TTS recurrence, stroke or transient ischaemic attack) were assessed at 30-day and 5-year follow-up. A total of 1533 TTS patients with known status regarding aspirin prescription at discharge were included. According to the adjusted analysis based on PS stratification, aspirin was not associated with a lower hazard of MACCE at 30-day [hazard ratio (HR) 1.24, 95% confidence interval (CI) 0.50–3.04, $P = 0.64$] or 5-year follow-up (HR 1.11, 95% CI 0.78–1.58, $P = 0.58$). These results were confirmed by sensitivity analyses performed with alternative PS-based methods, i.e. covariate adjustment and inverse probability of treatment weighting.

Conclusion

In the present study, no association was found between aspirin use in TTS patients and a reduced risk of MACCE at 30-day and 5-year follow-up. These findings should be confirmed in adequately powered randomized controlled trials.

ClinicalTrials.gov Identifier: NCT01947621.

Keywords

Takotsubo syndrome • Acute heart failure • Outcome • Medical therapy • Aspirin

Introduction

Takotsubo syndrome (TTS) mostly affects postmenopausal women and is usually preceded by an emotional or physical trigger.^{1–3} Clinical symptoms and signs at presentation, along with electrocardiographic (ECG) and laboratory changes, may mimic acute coronary syndrome (ACS) or acute heart failure.^{1,4–6} Although TTS has long been considered a benign condition, recent studies reported that it can be associated with significant adverse events both during hospitalization and after discharge.^{1,7–12} Therefore, there is a compelling need for an optimal preventive therapy to reduce the incidence of adverse events following TTS. According to recent data, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers have been reported to reduce mortality¹ and recurrence of TTS,¹³ while beta-blockers have not shown beneficial effects.^{1,14} However, data on therapeutic management of TTS

are mainly based on small case series,¹⁵ meta-analyses,^{13,16} or retrospective studies. There is still a lack of knowledge on optimal treatment strategies.

During the acute phase of TTS, a thrombogenic state may arise as a consequence of catecholamine-dependent ventricular dysfunction, platelet activation, and/or vasoconstriction.¹⁷ While anticoagulation therapy in the presence of left ventricular thrombus seems to be an appropriate choice, a recent retrospective study has also suggested a protective effect of antiplatelet therapy during index TTS hospitalization.¹⁸ However, uncertainty persists regarding an association between aspirin use and adverse events in TTS patients post-discharge. Therefore, the present study aimed to investigate the impact of aspirin use in a large TTS patient cohort [International Takotsubo (InterTAK) Registry, www.takotsubo-registry.com].

Methods

Data collection

The InterTAK Registry is an observational, prospective, and retrospective registry established at the University Hospital Zurich in 2011 in collaboration with 25 cardiovascular centres across nine countries.^{1,3} Patients were included in the registry between 2011 and 2014 based on the modified Mayo Clinic diagnostic criteria as previously reported^{1,19}: (i) transient abnormality of left ventricular wall motion extending beyond a single coronary artery perfusion territory, (ii) absence of obstructive coronary artery disease (CAD) or evidence of acute plaque rupture, (iii) presence of new ECG abnormalities or elevation in troponin, and (iv) absence of pheochromocytoma/myocarditis. Exceptions included coexisting CAD in whom wall motion abnormality was congruent with a single coronary artery territory, or death during the acute phase before documentation of wall motion recovery. Data on demographics, triggering factors, cardiovascular risk factors, haemodynamic and angiographic findings, ECG and echocardiography parameters, laboratory values, use of medications, in-hospital complications, and management were collected through standardized forms on admission or during revision of clinical charts.

For the purpose of the present analysis, patients were divided into two groups according to the prescription of aspirin at hospital discharge. Patients with unknown status regarding aspirin at discharge were excluded from the present study.

The local ethics committee or institutional review board at each participating site reviewed the study protocol. Most ethics committees waived the need for informed consent due to the partly retrospective nature of the study. Formal written consent was obtained from patients or their surrogates at participating centres whose ethics committees or institutional review boards required informed consent or if patients were included prospectively.

Study outcomes

Follow-up data were collected from clinical visits, medical charts, or telephone interviews as previously described.¹ The incidence of major adverse cardiac and cerebrovascular events [MACCE: a composite of all-cause death, TTS recurrence, stroke or transient ischaemic attack (TIA), or myocardial infarction (MI)] at 30-day and 5-year follow-up were the co-primary outcomes in the present analysis. Additionally, single components of MACCE at 5-year follow-up were analysed.

Statistical analysis

In the unadjusted analysis, continuous variables were summarized as mean \pm standard deviation, or median (1st–3rd quartile), and frequencies of categorical variables are presented as numbers with percentages. Categorical variables were compared with the Pearson chi-square test, continuous variables with the Student's *t*-test.

An adjusted analysis based on propensity score (PS) was performed. PS is the probability that each individual patient is included in the treatment group and is usually estimated via logistic regression based on the available baseline covariates. PS methods are used to compensate for the lack of proper statistical design and randomization in observational studies, like the present one. All variables expected to be associated with the outcomes of interest, or with both aspirin prescription and outcomes, are listed in online supplementary Table S1 and were used to construct the PS model.

The first step of the adjusted analysis was the treatment of missing data, which were present for a high number of variables (69 covariates out of 136). Assuming that data were missing at random and considering only the variables with less than 50% of missing data (the other covariates were excluded from the analyses),²⁰ we used polytomous logistic regression, logistic regression and predictive mean matching as multiple imputation techniques to fill in missing values, using the R *mice* package (version 3.6.0). We imputed five different datasets and the same statistical analyses were performed on each of them. After that, Rubin's rule²¹ was used to get pooled PS adjusted hazard ratio (HR) estimates and confidence intervals (CIs) for each endpoint (primary and secondary), according to each of the three methods described below: stratification, covariate adjustment and inverse probability of treatment weighting (IPTW) as sensitivity analysis.

With the method based on stratification, the total dataset is divided into mutually exclusive groups (strata), based on quantiles (in our case, tertiles) of the estimated PS; in this way, subjects from both arms are stratified in subsets that are defined by specific thresholds in PS.^{22,23} Then, all strata are included in a stratified proportional hazard Cox model to get an estimate of the HR for treatment, as previously described by Austin.²⁴

In the case of the covariate adjustment method, a Cox model is built with two predictors, given by the treatment indicator and PS itself.²⁵ An estimate of the treatment effect is then obtained based on the Cox model.

Finally, the IPTW technique involves assigning to each patient a stabilized weight equal to $(1-p)/(1-PS)$ if a control, or equal to p/PS if a treated patient,²⁰ where *p* is the probability of treatment without any covariate and PS is the value of the PS for that patient. The choice of stabilized weights allowed us to work with a pseudo-sample (as large as the sum of the weights) that has approximately the same size as the actual one.²⁶ Then, the weights were included in the survival analysis to estimate two adjusted Kaplan–Meier curves²⁷ (one for each treatment). The weights were also used to estimate the parameters of the Cox model, and in particular the HR.²⁸

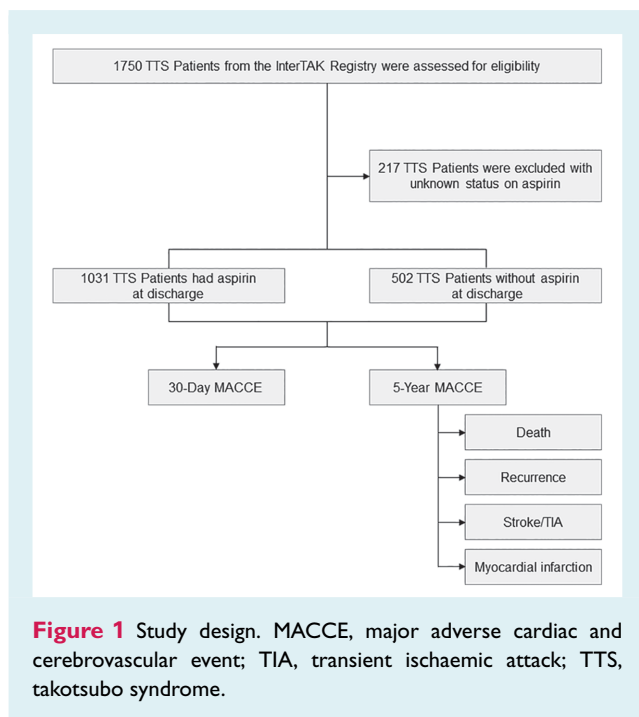
No association of any continuous predictor and aspirin prescription departed from linearity, as assessed through the statistical significance of quadratic and cubic terms.

The adjusted statistical analysis was performed using R 3.5.1 and some of its packages,^{29,30} notably *mice* package (version 3.6.0), *rms* (version 5.1–3.1) and *survival* (version 2.44–1.1).

Results

Study population

Out of 1750 patients in the InterTAK Registry, 1533 with documented status regarding aspirin at discharge were included in the present analysis (Figure 1). The mean age was 66.4 ± 13.1 years and 1382 (90.2%) were female. A total of 989 (65.8%) patients had hypertension, 221 (14.7%) diabetes mellitus, and 480 (32.0%) hypercholesterolaemia. ST-segment elevation was observed in 606 (43.5%) patients on admission. An emotional trigger was identified in 447 (29.2%) patients and a physical trigger in 533 (34.8%). Patient characteristics of the whole study cohort and of TTS patients with and without aspirin at discharge are summarized in Table 1. Unadjusted outcomes are reported in Table 2, showing a higher risk of 5-year death for patients on aspirin and no difference for the other endpoints.



Adjusted comparison using propensity score with the stratification method

According to the PS stratification method, aspirin was not associated with a reduced hazard of MACCE at 30-day (HR 1.24, 95% CI 0.50–3.04, $P = 0.64$) or 5-year follow-up (HR 1.11, 95% CI 0.78–1.58, $P = 0.58$). Furthermore, no significant differences were observed for the single components of MACCE, including death (HR 1.36, 95% CI 0.79–2.34, $P = 0.27$), TTS recurrence (HR 0.53, 95% CI 0.27–1.03, $P = 0.06$), stroke/TIA (HR 1.52, 95% CI 0.65–3.54, $P = 0.33$), or MI (HR 3.28, 95% CI 0.38–28.28, $P = 0.28$) (Table 2).

Sensitivity analysis: propensity score covariate adjustment and propensity score inverse probability of treatment weighting method

Propensity score IPTW and PS covariate adjustment methods did not show any association between aspirin and a risk reduction for MACCE or its single components (Table 2), except for TTS recurrence, which showed some weak association. The survival analysis for MACCE and death based on IPTW results confirmed these findings as shown in Figure 2, which depicts the Kaplan–Meier curves of the two groups crossing each other.

In order to verify that the application of the IPTW method allowed to achieve a gain in similarity between the active and control groups, we plotted two ‘mirrored’ histograms showing the distribution of PS (averaged on five imputed datasets) within each treatment group on the true and the pseudo populations (online supplementary Figure 1). After the application of the IPTW method,

the distribution of PS between groups looks more symmetrical: treated PSs are ‘shifted’ towards 0, while untreated PSs towards 1. The difference in frequency within each PS interval between the active and control groups is due to the different sizes of the two groups, 1031 treated subjects and 502 untreated ones.

Discussion

The increased awareness of TTS has resulted in a higher recognition of TTS among physicians.³¹ However, there is still a lack of evidence for specific TTS treatments.

The present study found that aspirin at hospital discharge did not relate to short- or long-term prognosis in a large population of TTS patients. The incidence of MACCE in patients discharged with aspirin, who were not randomized but were adjusted for a higher burden of co-morbidities with PS methods, was not significantly different compared to patients without aspirin, both at short and long-term follow-up. Furthermore, single components of MACCE were similar at 5 years. Presence of CAD at baseline did not affect these results.

Takotsubo syndrome pathophysiology is hypothesized to be mediated by an abrupt surge of catecholamines leading to ventricular dysfunction.³² An increased cardiac sympathetic activity is known to be associated with unfavourable outcomes in cardiovascular diseases.^{33–35} Of note, the catecholaminergic surge may activate platelets and proinflammatory pathways, setting the stage for the use of antiplatelet agents such as aspirin. The protective effect of aspirin in acute cardiovascular diseases, however, is mainly related to the reduction of thrombotic events induced by platelet activation following plaque erosion or rupture. These mechanisms do not appear to play a significant role in TTS, as it appears that TTS mainly involves the microcirculatory system, thus this explains the lack of potential benefit associated with aspirin in this syndrome.³⁶

Aspirin acts both as an antithrombotic as well as an anti-inflammatory agent, suppressing the production of prostaglandins, thromboxane, and decreasing plasma levels of several inflammatory biomarkers, posing a potential prognostic benefit in TTS. Nevertheless, a negative interaction has been shown between aspirin (related to dose) and survival benefit of ACE inhibitor therapy in patients admitted for heart failure and could have implications in TTS patients as well.³⁷ In a recent study of Dias *et al.*,¹⁸ a beneficial effect of aspirin on an in-hospital combined endpoint has been reported when given at the time of TTS index event. However, this effect may result from the combined therapy of aspirin and clopidogrel together. Moreover, the authors evaluated only hospital events in a relatively small sample size, which may have produced incidental findings.

In line with our results, Fazio *et al.*³⁸ demonstrated a lack of benefit of in-hospital aspirin administration on both hospitalization length and ejection fraction improvement in a relatively small number of TTS patients. Of note, we focused on aspirin use after hospital discharge, also adjusting for major confounding factors with PS-stratified analysis, and similarly we could not demonstrate an association between aspirin and improved outcome at follow-up. We found some evidence of weak association between aspirin

Table 1 Characteristics of takotsubo syndrome patients according to aspirin prescription at discharge

Characteristic	All (n = 1533)	Aspirin (n = 1031)	No aspirin (n = 502)	P-value
Demographics				
Female sex, n/total n (%)	1382/1533 (90.2)	926/1031 (89.8)	456/502 (90.8)	0.53
Age, years	66.4 ± 13.1 (n = 1533)	68.0 ± 12.1 (n = 1031)	64.0 ± 13.6 (n = 502)	<0.001
Triggers, n/total n (%)				
Physical	533/1533 (34.8)	334/1031 (32.4)	199/502 (39.6)	0.005
Emotional	447/1533 (29.2)	319/1031 (30.9)	128/502 (25.5)	0.028
Cardiovascular risk factors, n/total n (%)				
Hypertension	989/1502 (65.8)	698/1009 (69.2)	291/493 (59.0)	<0.001
Diabetes mellitus	221/1504 (14.7)	161/1011 (15.9)	60/493 (12.2)	0.054
Hypercholesterolaemia	480/1499 (32.0)	347/1006 (34.5)	133/493 (27.0)	0.003
Haemodynamic and angiographic findings				
CAD ^a , n/total n (%)	217/1418 (15.3)	180/970 (18.6)	37/448 (8.3)	<0.001
Apical type, n/total n (%)	1252/1533 (81.7)	853/1031 (82.7)	399/502 (79.5)	0.12
Heart rate, bpm	86.8 ± 21.7 (n = 1294)	86.4 ± 21.4 (n = 869)	87.5 ± 22.3 (n = 425)	0.39
Systolic blood pressure, mmHg	131.1 ± 28.5 (n = 1219)	131.9 ± 28.1 (n = 873)	129.6 ± 29.4 (n = 419)	0.17
Left ventricular ejection fraction ^b , %	41.5 ± 11.8 (n = 1407)	41.5 ± 11.7 (n = 937)	41.4 ± 12.0 (n = 470)	0.89
Left ventricular end-diastolic pressure, mmHg	21.4 ± 8.1 (n = 926)	21.8 ± 8.1 (n = 628)	20.5 ± 8.0 (n = 298)	0.017
ECG on admission, n/total n (%)				
Sinus rhythm	1291/1399 (92.3)	879/945 (93.0)	412/454 (90.7)	0.14
ST-segment elevation	606/1394 (43.5)	433/941 (46.0)	173/453 (38.2)	0.006
ST-segment depression	106/1394 (7.6)	74/941 (7.9)	32/453 (7.1)	0.60
T-wave inversion	581/1394 (41.7)	388/941 (41.2)	193/453 (42.6)	0.63
Laboratory profile on admission, median (IQR)				
Troponin, factor increase in ULN ^c	7.20 (2.20–24.0) (n = 1289)	7.45 (2.2–22.1) (n = 886)	7.33 (2.14–24.0) (n = 403)	0.89
Creatine kinase, factor increase in ULN	0.85 (0.52–1.48) (n = 1075)	0.84 (0.53–1.44) (n = 728)	0.89 (0.52–1.54) (n = 347)	0.58
BNP, factor increase in ULN ^d	6.20 (2.14–15.78) (n = 410)	5.50 (2.11–15.00) (n = 271)	6.25 (2.25–17.50) (n = 139)	0.14
C-reactive protein, mg/L	4.00 (1.40–11.98) (n = 1043)	4.00 (1.50–11.00) (n = 695)	3.60 (1.13–12.50) (n = 348)	0.07
White blood cell count, 10 ³ /μL	9.73 (7.46–12.70) (n = 1317)	10.65 (7.43–12.40) (n = 886)	9.50 (7.30–12.80) (n = 431)	0.94
Medication at discharge, n/total n (%)				
ACE inhibitor or ARB	1215/1533 (79.3)	852/1031 (82.6)	363/502 (72.3)	<0.001
Beta-blocker	1197/1533 (78.1)	832/1031 (80.7)	365/502 (72.7)	<0.001
Coumarin	126/1533 (8.2)	52/1031 (5.0)	74/502 (14.7)	<0.001
Statin	786/1533 (51.3)	653/1031 (63.3)	133/502 (26.5)	<0.001
In-hospital complications and management, n/total n (%)				
Catecholamine use	145/1528 (9.5)	83/1027 (8.1)	62/501 (12.4)	0.007
Cardiogenic shock	115/1511 (7.6)	65/1013 (6.4)	50/498 (10.0)	0.013
Invasive and non-invasive ventilation	218/1528 (14.3)	121/1027 (11.8)	97/501 (19.4)	<0.001
Cardiopulmonary resuscitation	104/1528 (6.8)	57/1027 (5.6)	47/501 (9.4)	0.005

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BNP, B-type natriuretic peptide; CAD, coronary artery disease; ECG, electrocardiogram; IQR, interquartile range; ULN, upper limit of normal.

^aCoexisting CAD during acute hospitalization.

^bInformation from catheterization or echocardiography, if both available: catheterization.

^cIncluded in this category are the ULN range for troponin T, high-sensitivity troponin T, and troponin I.

^dIncluded in this category are the ULN range for B-type natriuretic peptide and N-terminal pro-B-type natriuretic peptide.

and only TTS recurrence; such weak association is detected by the covariate adjustment and the IPTW methods and not by the stratification method. Therefore, this potential association should be interpreted carefully, considering the lack of a supporting pathophysiological mechanism. Since any potential benefit should be pondered with the inevitable higher bleeding risk in patients

taking aspirin on a long-term basis, the routine use of aspirin should not be encouraged especially in patients at high risk for bleeding.³⁹

Our results suggest that TTS *per se* does not represent an indication for treatment with aspirin. Aspirin treatment might be withdrawn even during hospitalization once the clinical picture of TTS has been unmasked, unless there are coexisting co-morbidities

Table 2 Outcomes according to aspirin therapy before and after adjustment according to propensity score methods

	Crude event rate		Unadjusted HR (95% CI)	PS stratification, HR (95% CI)	PS covariate adjustment, HR (95% CI)	PS with IPTW, HR (95% CI)
	Aspirin (n = 1031)	No aspirin (n = 502)				
30-day MACCE ^a	21/1031 (2.0)	9/502 (1.8)	0.89 (0.41–1.95) P = 0.78	1.24 (0.50–3.04) P = 0.64	1.26 (0.52–3.03) P = 0.61	1.55 (0.65–3.67) P = 0.32
5-year MACCE ^a	140/1031 (13.6)	46/502 (9.2)	1.15 (0.81–1.68) P = 0.41	1.11 (0.78–1.58) P = 0.58	1.07 (0.73–1.56) P = 0.73	1.11 (0.78–1.58) P = 0.58
Death	76/1031 (7.4)	21/502 (4.2)	1.41 (0.86–2.26) P = 0.18	1.36 (0.79–2.34) P = 0.27	1.37 (0.79–2.41) P = 0.27	1.64 (0.89–3.03) P = 0.11
Recurrence	31/1031 (3.0)	17/502 (3.4)	0.65 (0.26–1.17) P = 0.15	0.53 (0.27–1.03) P = 0.06	0.48 (0.25–0.92) P = 0.03	0.47 (0.26–0.83) P = 0.01
Stroke or TIA	32/1031 (3.1)	9/502 (1.8)	1.38 (0.66–2.89) P = 0.39	1.52 (0.65–3.54) P = 0.33	1.45 (0.63–3.35) P = 0.39	1.41 (0.66–3.03) P = 0.37
Myocardial infarction	8/1031 (0.8)	1/502 (0.2)	3.11 (0.38–24.42) P = 0.29	3.28 (0.38–28.28) P = 0.28	4.08 (0.43–38.6) P = 0.22	5.93 (0.35–100.1) P = 0.22

CI, confidence interval; HR, hazard ratio; IPTW, inverse probability of treatment weighting; MACCE, major adverse cardiac and cerebrovascular event; PS, propensity score; TIA, transient ischaemic attack.

^aA composite of death, takotsubo syndrome recurrence, stroke or TIA, or myocardial infarction.

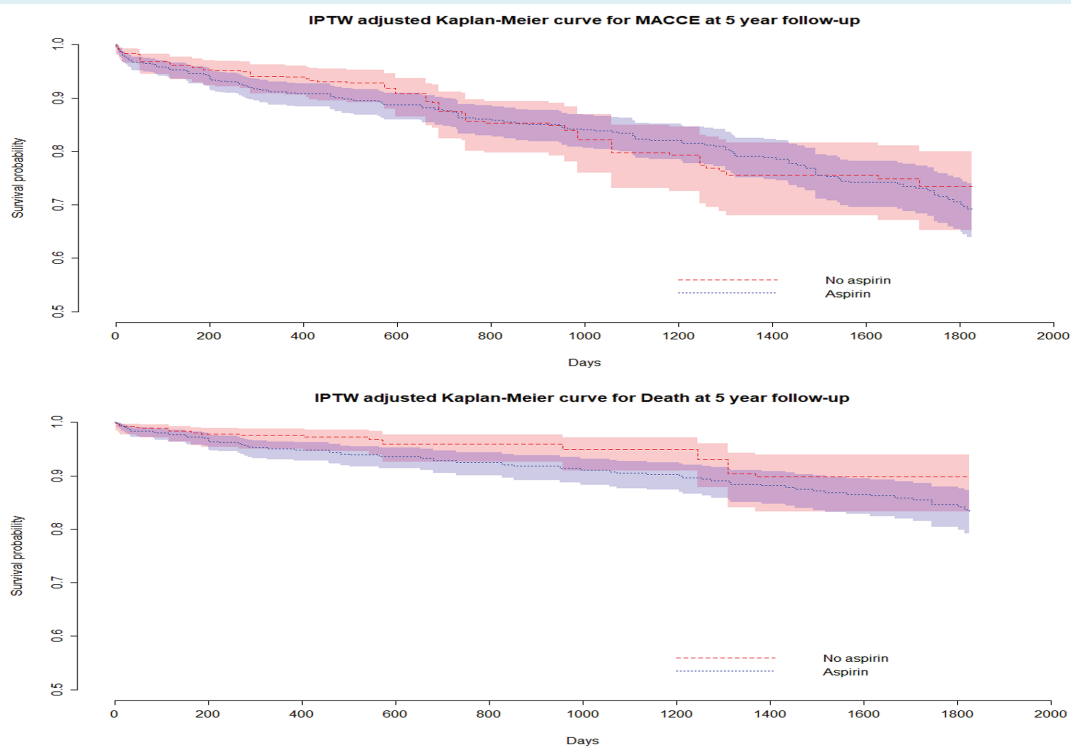


Figure 2 Inverse probability of treatment weighting (IPTW) adjusted Kaplan–Meier analysis. Coloured bands represent the 95% pointwise confidence bands. MACCE, major adverse cardiac and cerebrovascular event.

that confer a high atherosclerotic risk and require antiplatelet therapy according to current guidelines.

Study limitations

The present study is not a randomized controlled trial, but we tried to address this shortcoming using PS, which may nonetheless adjust only for recorded variables and not for the missing ones. Given the low prevalence of TTS, it is challenging to obtain robust data on treatment or to conduct comparative randomized controlled trials. Therefore, the application of PS methods is currently state of the art in this setting.

A methodological limitation of the study is that we mostly observed the absence of aspirin effects. As it is well known, absence of evidence is not evidence of absence, and a statistical proof of the lack of aspirin effect should properly be conducted within an equivalence approach using appropriately designed clinical trials, whereas it is not possible to do so using only observational studies.

Performance of PS was tested by assessing standardized differences (SDs) before and after PS using IPTW on the covariates considered, with satisfactory results (online supplementary Table 1): in fact, the computation of SDs demonstrate that even though some SDs increased from the unadjusted to the adjusted population, this led to an overall decrease in all SDs adjusted with IPTW, so that almost all variables have a SD lower than 0.1 between treatment groups. Regarding non-linearity, residuals are symmetrically distributed around 0 and lowess interpolation within each plot does not show any particular non-linear relationships (online supplementary Figure S1). Moreover, in the stratification analysis, we used three strata, with a potential higher risk of bias; however, the results are consistent with the other two analyses, confirming the overall strength of our model.

Proper sample size calculation showed that this study is formally underpowered for main outcomes, although it should be remembered that this is the largest available registry on this topic. This is particularly true for MI, which occurred only in nine patients leading to large CI after PS adjustment.

The dose-dependent detrimental interaction of aspirin with ACE inhibitor therapy survival benefit makes the net effect of aspirin alone not completely predictable in TTS patients in whom both therapies are usually co-administered.

Conclusions

In the present analysis, after adjusting for potential confounding factors, we found no evidence that aspirin at discharge is associated with a reduced risk of MACCE at short- or long-term follow-up in TTS patients. These findings should be confirmed in adequately powered randomized controlled trials.

Supplementary Information

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

Table S1. List of covariates used to calculate the propensity score.

Table S2. Standardized mean differences of the covariates used before and after inverse probability of treatment weighting adjustment.

Figure S1. Distribution of propensity score in the two groups before and after inverse probability of treatment weighting adjustment.

Funding

C.T. has been supported by the H.H. Sheikh Khalifa bin Hamad Al-Thani Research Programme and the Swiss Heart Foundation. The Inter-TAK Registry is supported by The Biss Davies Charitable Trust. The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflict of interest: none declared.

References

- Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, Cammann VL, Sarcon A, Geyer V, Neumann CA, Seifert B, Hellermann J, Schwyzer M, Eisenhardt K, Jenewein J, Franke J, Katus HA, Burgdorf C, Schunkert H, Moeller C, Thiele H, Bauersachs J, Tschope C, Schultheiss HP, Laney CA, Rajan L, Michels G, Pfister R, Ukena C, Bohm M, Erbel R, Cuneo A, Kuck KH, Jacobshagen C, Hasenfuss G, Karakas M, Koenig W, Rottbauer W, Said SM, Braun-Dullaeus RC, Cuculi F, Banning A, Fischer TA, Vasankari T, Airaksinen KE, Fijalkowski M, Rynkiewicz A, Pawlak M, Opolski G, Dworakowski R, MacCarthy P, Kaiser C, Osswald S, Galiuto L, Crea F, Dichtl W, Franz WM, Empen K, Felix SB, Delmas C, Lairez O, Erne P, Bax JJ, Ford I, Ruschitzka F, Prasad A, Luscher TF. Clinical features and outcomes of takotsubo (stress) cardiomyopathy. *N Engl J Med* 2015;**373**:929–938.
- Kato K, Lyon AR, Ghadri JR, Templin C. Takotsubo syndrome: aetiology, presentation and treatment. *Heart* 2017;**103**:1461–1469.
- Ghadri JR, Cammann VL, Templin C. The International Takotsubo Registry: rationale, design, objectives, and first results. *Heart Fail Clin* 2016;**12**:597–603.
- Gianni M, Dentali F, Grandi AM, Sumner G, Hiralal R, Lonn E. Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review. *Eur Heart J* 2006;**27**:1523–1529.
- Ghadri JR, Ruschitzka F, Luscher TF, Templin C. Takotsubo cardiomyopathy: still much more to learn. *Heart* 2014;**100**:1804–1812.
- Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, Cammann VL, Crea F, Galiuto L, Desmet W, Yoshida T, Manfredini R, Eitel I, Kosuge M, Nef HM, Deshmukh A, Lerman A, Bossone E, Citro R, Ueyama T, Corrado D, Kurisu S, Ruschitzka F, Winchester D, Lyon AR, Omerovic E, Bax JJ, Meimoun P, Tarantini G, Rihal C, S Y-H, Migliore F, Horowitz JD, Shimokawa H, Luscher TF, Templin C. International expert consensus document on takotsubo syndrome (part I): clinical characteristics, diagnostic criteria, and pathophysiology. *Eur Heart J* 2018;**39**:2032–2046.
- Ghadri JR, Kato K, Cammann VL, Gili S, Jurisic S, Di Vece D, Candrea A, Ding KJ, Micek J, Szawan KA, Bacchi B, Bianchi R, Levinson RA, Wischniewsky M, Seifert B, Schlossbauer SA, Citro R, Bossone E, Munzel T, Knorr M, Heiner S, D'Ascenzo F, Franke J, Sarcon A, Napp LC, Jaguszewski M, Noutsias M, Katus HA, Burgdorf C, Schunkert H, Thiele H, Bauersachs J, Tschope C, Pieske BM, Rajan L, Michels G, Pfister R, Cuneo A, Jacobshagen C, Hasenfuss G, Karakas M, Koenig W, Rottbauer W, Said SM, Braun-Dullaeus RC, Banning A, Cuculi F, Kobza R, Fischer TA, Vasankari T, Airaksinen KEJ, Opolski G, Dworakowski R, MacCarthy P, Kaiser C, Osswald S, Galiuto L, Crea F, Dichtl W, Empen K, Felix SB, Delmas C, Lairez O, El-Battrawy I, Akin I, Borggrefe M, Horowitz J, Kozel M, Tousek P, Widimsky P, Gilyarova E, Shilova A, Gilyarov M, Winchester DE, Ukena C, Bax JJ, Prasad A, Bohm M, Luscher TF, Ruschitzka F, Templin C. Long-term prognosis of patients with takotsubo syndrome. *J Am Coll Cardiol* 2018;**72**:874–882.
- Elesber AA, Prasad A, Lennon RJ, Wright RS, Lerman A, Rihal CS. Four-year recurrence rate and prognosis of the apical ballooning syndrome. *J Am Coll Cardiol* 2007;**50**:448–452.

9. Sharkey SW, Windenburg DC, Lesser JR, Maron MS, Hauser RG, Lesser JN, Haas TS, Hodges JS, Maron BJ. Natural history and expansive clinical profile of stress (tako-tsubo) cardiomyopathy. *J Am Coll Cardiol* 2010;**55**:333–341.
10. Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, Cammann VL, Crea F, Galiuto L, Desmet W, Yoshida T, Manfredini R, Eitel I, Kosuge M, Nef HM, Deshmukh A, Lerman A, Bossone E, Citro R, Ueyama T, Corrado D, Kurisu S, Ruschitzka F, Winchester D, Lyon AR, Omerovic E, Bax JJ, Meimoun P, Tarantini G, Rihal C, S Y-H, Migliore F, Horowitz JD, Shimokawa H, Luscher TF, Templin C. International expert consensus document on takotsubo syndrome (part II): diagnostic workup, outcome, and management. *Eur Heart J* 2018;**39**:2047–2062.
11. Di Vece D, Citro R, Cammann VL, Kato K, Gili S, Szawan KA, Micek J, Jurisic S, Ding KJ, Bacchi B, Schwyzer M, Candrea A, Bossone E, D'Ascenzo F, Sarcon A, Franke J, Napp LC, Jaguszewski M, Noutsias M, Munzel T, Knorr W, Wagner S, Katus HA, Burgdorf C, Schunkert H, Thiele H, Bauersachs J, Tschope C, Pieske B, Rajan L, Michels G, Pfister R, Cuneo A, Jacobshagen C, Hasenfubeta G, Karakas M, Koenig W, Rottbauer W, Said SM, Braun-Dullaeus RC, Banning A, Cuculi F, Kobza R, Fischer TA, Vasankari T, Airaksinen KE, Opolski G, Dworakowski R, MacCarthy P, Kaiser C, Osswald S, Galiuto L, Crea F, Dichtl W, Empen K, Felix SB, Delmas C, Lairez O, El-Batraway I, Akin I, Borggrefe M, Gilyarova E, Shilova A, Gilyarov M, Horowitz J, Kozel M, Tousek P, Widimsky P, Winchester DE, Ukena C, Di Mario C, Prasad A, Bohm M, Bax JJ, Luscher T, Ruschitzka F, Ghadri JR, Templin C. Outcomes associated with cardiogenic shock in Takotsubo syndrome: results from the International Takotsubo registry. *Circulation* 2019;**139**:413–415.
12. Kato K, Sakai Y, Ishibashi I, Himi T, Fujimoto Y, Kobayashi Y. Predictors of in-hospital cardiac complications in patients with takotsubo syndrome. *Heart Vessels* 2018;**33**:1214–1219.
13. Singh K, Carson K, Usmani Z, Sawhney G, Shah R, Horowitz J. Systematic review and meta-analysis of incidence and correlates of recurrence of takotsubo cardiomyopathy. *Int J Cardiol* 2014;**174**:696–701.
14. Isogai T, Matsui H, Tanaka H, Fushimi K, Yasunaga H. Early beta-blocker use and in-hospital mortality in patients with takotsubo cardiomyopathy. *Heart* 2016;**102**:1029–1035.
15. Santoro F, Ieva R, Ferraretti A, Ienco V, Carpagnano G, Lodispoto M, Di Biase L, Di Biase M, Brunetti ND. Safety and feasibility of levosimendan administration in takotsubo cardiomyopathy: a case series. *Cardiovasc Ther* 2013;**31**:e133–e137.
16. Santoro F, Ieva R, Musaico F, Ferraretti A, Triggiani G, Tarantino N, Di Biase M, Brunetti ND. Lack of efficacy of drug therapy in preventing takotsubo cardiomyopathy recurrence: a meta-analysis. *Clin Cardiol* 2014;**37**:434–439.
17. Cecchi E, Parodi G, Giglioli C, Passantino S, Bandinelli B, Liotta AA, Bellandi B, Cioni G, Costanzo M, Abbate R, Gensini GF, Antonucci D, Mannini L. Stress-induced hyperviscosity in the pathophysiology of takotsubo cardiomyopathy. *Am J Cardiol* 2013;**111**:1523–1529.
18. Dias A, Franco E, Koshkelashvili N, Bhalla V, Pressman GS, Hebert K, Figueredo VM. Antiplatelet therapy in takotsubo cardiomyopathy: does it improve cardiovascular outcomes during index event? *Heart Vessels* 2016;**31**:1285–1290.
19. Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (tako-tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. *Am Heart J* 2008;**155**:408–417.
20. Morris TP, White IR, Royston P. Tuning multiple imputation by predictive mean matching and local residual draws. *BMC Med Res Methodol* 2014;**14**:75.
21. Leyrat C, Seaman SR, White IR, Douglas I, Smeeth L, Kim J, Resche-Rigon M, Carpenter JR, Williamson EJ. Propensity score analysis with partially observed covariates: how should multiple imputation be used? *Stat Methods Med Res* 2017;**28**:3–19.
22. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivar Behav Res* 2011;**46**:399–424.
23. Haukoos JS, Lewis RJ. The propensity score. *JAMA* 2015;**314**:1637–1638.
24. Austin PC. A tutorial and case study in propensity score analysis: an application to estimating the effect of in-hospital smoking cessation counseling on mortality. *Multivar Behav Res* 2011;**46**:119–151.
25. Elze MC, Gregson J, Baber U, Williamson E, Sartori S, Mehran R, Nichols M, Stone GW, Pocock SJ. Comparison of propensity score methods and covariate adjustment: evaluation in 4 cardiovascular studies. *J Am Coll Cardiol* 2017;**69**:345–357.
26. Xu S, Ross C, Raebel MA, Shetterly S, Blanchette C, Smith D. Use of stabilized inverse propensity scores as weights to directly estimate relative risk and its confidence intervals. *Value Health* 2010;**13**:273–277.
27. Xie J, Liu C. Adjusted Kaplan-Meier estimator and log-rank test with inverse probability of treatment weighting for survival data. *Stat Med* 2005;**24**:3089–3110.
28. Buchanan AL, Hudgens MG, Cole SR, Lau B, Adimora AA; Women's Interagency HIV Study. Worth the weight: using inverse probability weighted Cox models in AIDS research. *AIDS Res Hum Retroviruses* 2014;**30**:1170–1177.
29. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. <https://www.r-project.org> [accessed 25 November 2019].
30. Maechler M, Rousseeuw P, Struyf A, Hubert M, Hornik K. (2013). *Cluster: Cluster Analysis Basics and Extensions. R package version 1.14.4*.
31. Ghadri JR, Cammann VL, Napp LC, Jurisic S, Diekmann J, Bataiosu DR, Seifert B, Jaguszewski M, Sarcon A, Neumann CA, Geyer V, Prasad A, Bax JJ, Ruschitzka F, Luscher TF, Templin C; International Takotsubo (InterTAK) Registry. Differences in the clinical profile and outcomes of typical and atypical takotsubo syndrome: data from the International Takotsubo Registry. *JAMA Cardiol* 2016;**1**:335–340.
32. Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, Gerstenblith G, Wu KC, Rade JJ, Bivalacqua TJ, Champion HC. Neurohumoral features of myocardial stunning due to sudden emotional stress. *N Engl J Med* 2005;**352**:539–548.
33. Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, Francis GS, Simon AB, Rector T. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med* 1984;**311**:819–823.
34. Kaye DM, Lefkowitz J, Jennings GL, Bergin P, Broughton A, Esler MD. Adverse consequences of high sympathetic nervous activity in the failing human heart. *J Am Coll Cardiol* 1995;**26**:1257–1263.
35. Brunner-La Rocca HP, Esler MD, Jennings GL, Kaye DM. Effect of cardiac sympathetic nervous activity on mode of death in congestive heart failure. *Eur Heart J* 2001;**22**:1136–1143.
36. Luscher TF, Templin C. Is takotsubo syndrome a microvascular acute coronary syndrome? Towards of a new definition. *Eur Heart J* 2016;**37**:2816–2820.
37. Guazzi M, Brambilla R, Reina G, Tumminello G, Guazzi MD. Aspirin-angiotensin-converting enzyme inhibitor coadministration and mortality in patients with heart failure: a dose-related adverse effect of aspirin. *Arch Intern Med* 2003;**163**:1574–1579.
38. Fazio G, Pizzuto C, Barbaro G, Sutura L, Incalcaterra E, Evola G, Azzarelli S, Palecek T, Di Gesaro G, Cascio C, Novo G, Akashi YJ, Novo S. Chronic pharmacological treatment in takotsubo cardiomyopathy. *Int J Cardiol* 2008;**127**:121–123.
39. Fletcher RH. Review: aspirin for CVD primary prevention increases gastrointestinal bleeding and hemorrhagic stroke. *Ann Intern Med* 2016;**165**:C17.