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

# Impact of Aspirin on Takotsubo Syndrome: A Propensity Score Based Analysis of the InterTAK Registry

**Running title:** Aspirin in Takotsubo syndrome

Fabrizio D'Ascenzo[1], MD, PhD; Sebastiano Gili[2], MD; Maurizio Bertaina[1], MD; Mario Iannaccone[1], MD; Victoria L. Cammann[3], MD; Davide Di Vece[3], MD; Ken Kato[3], MD, PhD; Andrea Saglietto[1], MD; Konrad A. Szawan[3], MD; Antonio H. Frangieh[4,5], MD; Beatrice Boffini[2]; Margherita Annaratone[6], MS; Annahita Sarcon[7], MD; Rena A Levinson[3,8], BS; Jennifer Franke[9], MD; L. Christian Napp[10], MD; Milosz Jaguszewski[11], MD, PhD; Michel Noutsias[12], MD; Thomas Münzel[13], MD; Maike Knorr[13], MD; Susanne Heiner[13], MD; Hugo A. Katus[9], MD; Christof Burgdorf[14], MD; Heribert Schunkert[4,5], MD; Holger Thiele[15], MD; Johann Bauersachs[10], MD; Carsten Tschöpe[16], MD; Burkert M. Pieske[16], MD; Lawrence Rajan[17], MD; Guido Michels[18], MD; Roman Pfister[18], MD; Alessandro Cuneo[19], MD; Claudius Jacobshagen[20], MD; Gerd Hasenfuß[20], MD; Mahir Karakas[21,22], MD; Wolfgang Koenig[4,5], MD; Wolfgang Rottbauer[23], MD; Samir M. Said[24], MD; Ruediger C. Braun-Dullaeus[24], MD; Adrian Banning[25], MD; Florim Cuculi[26], MD; Richard Kobza[26], MD; Thomas A. Fischer[27], MD; Tuija Vasankari[28], MD; K.E. Juhani Airaksinen[28], MD, PhD; Grzegorz Opolski[29], MD, PhD; Rafal Dworakowski[30], MD; Philip MacCarthy[30], MD, PhD; Christoph Kaiser[31], MD; Stefan Osswald[31], MD; Leonarda Galiuto[32], MD, PhD; Filippo Crea[32], MD; Wolfgang Dichtl[33], MD, PhD; Wolfgang M. Franz[33], MD; Klaus Empen[34,35], MD; Stephan B. Felix[34,35], MD; Clément Delmas[36], MD; Olivier Lairez[36], MD, PhD; Ibrahim El-Battrawy[37,38], MD; Ibrahim Akin[37,38], MD; Martin Borggrefe[37,38], MD; John D. Horowitz[39], MBBS, PhD; Martin Kozel[40], MD; Petr Tousek[40], MD; Petr Widimský[40], MD, PhD; Ekaterina Gilyarova[41], MD; Alexandra Shilova[41], MD, PhD; Mikhail Gilyarov[41], MD, PhD; Giuseppe Biondi-Zoccai[42], MD, MStat; David E. Winchester[43], MD; Christian Ukena[44], MD; Michael Neuhaus[45], MD; Jeroen J. Bax[46], MD, PhD; Abhiram Prasad[47], MD;, MD; Carlo Di Mario[49], MD, PhD; Michael Böhm[44], MD; Mauro Gasparini[6], PhD ; Frank Ruschitzka[3], MD; Eduardo Bossone[50], MD, PhD; Rodolfo Citro[51], MD, PhD; Mauro Rinaldi[1], MD; Gaetano Maria De Ferrari[48]; Thomas Lüscher[52,53], MD; Jelena R. Ghadri[3], MD; Christian Templin[3], MD, PhD

[1] Division of Cardiology, Department of Medical Sciences, AOU Città della Salute e della Scienza, University of Turin, Turin, Italy
[2] Centro cardiologico Monzino, IRCCS, Milan, Italy
[3] University Heart Center, Department of Cardiology, University Hospital Zurich, Zurich, Switzerland
[4] Deutsches Herzzentrum München, Technische Universität München, Munich, Germany
[5] DZHK (German Centre for Cardiovascular Research), partner site Munich Heart Alliance, Munich, Germany
[6] Department of Mathematical Sciences, Politecnico di Torino, Turin, Italy
[7] Section of Cardiac Electrophysiology, Department of Medicine, University of California-San Francisco, San Francisco, CA, USA
[8] Division of Biological Sciences, University of California San Diego, San Diego, CA, USA
[9] Department of Cardiology, Heidelberg University Hospital, Heidelberg, Germany
[10] Department of Cardiology and Angiology, Hannover Medical School, Hannover, Germany
[11] First Department of Cardiology, Medical University of Gdansk, Gdansk, Poland
[12] Department of Internal Medicine III, Division of Cardiology, Angiology and Intensive Medical Care, University Hospital Halle, Martin-Luther-University Halle, Halle (Saale), Germany
[13] Center for Cardiology, Cardiology 1, University Medical Center Mainz, Mainz, Germany
[14] Heart and Vascular Centre Bad Bevensen, Bad Bevensen, Germany
[15] Heart Center Leipzig – University Hospital, Department of Internal Medicine/Cardiology, Leipzig, Germany
[16] Department of Cardiology, Charité, Campus Rudolf Virchow, Berlin, Germany
[17] TJ Health Partners Heart and Vascular, Glasgow, KY, USA
[18] Department of Internal Medicine III, Heart Center University of Cologne, Cologne, Germany
[19] Krankenhaus "Maria Hilf" Medizinische Klinik, Stadtlohn, Germany
[20] Clinic for Cardiology and Pneumology, Georg August University Goettingen, Goettingen, Germany
[21] Department of General and Interventional Cardiology, University Heart Center Hamburg, Hamburg, Germany
[22] DZHK (German Centre for Cardiovascular Research), partner site Hamburg/Kiel/Luebeck, Hamburg, Germany
[23] Department of Internal Medicine II – Cardiology, University of Ulm, Medical Center, Ulm, Germany
[24] Internal Medicine/Cardiology, Angiology, and Pneumology, Magdeburg University, Magdeburg, Germany
[25] Department of Cardiology, John Radcliffe Hospital, Oxford University Hospitals, Oxford, United Kingdom
[26] Department of Cardiology, Kantonsspital Lucerne, Lucerne, Switzerland
[27] Department of Cardiology, Kantonsspital Winterthur, Winterthur, Switzerland
[28] Heart Center, Turku University Hospital and University of Turku, Turku, Finland
[29] Department of Cardiology, Medical University of Warsaw, Warsaw, Poland

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

**Correspondence to:**
Fabrizio D’Ascenzo, MD, PhD
Interventional Cardiologist
Division of Cardiology, Department of Medical Sciences
AOU Citta della Salute e della Scienza, University of Turin
Corso Bramante 88-90,
10126, Turin, Italy
Phone: +39 0116334446
E-mail: fabrizio.dascenzo@gmail.com

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**ABSTRACT**

**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 Registry (InterTAK Registry) were categorized into two groups based on aspirin prescription at discharge. A comparison of clinical outcomes between the two groups was performed using an adjusted analysis with propensity score 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 ischemic attack [TIA]) 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 number: 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 inhibitors or angiotensin-receptor blockers have been reported to reduce mortality[1] 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 data. There is still a lack of knowledge available 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 anti-platelet 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 Registry (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 centers across 9 countries.[1, 3] Patients were included in the registry between 2011 and 2014 based on 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 electrocardiographic abnormalities or elevation in troponin and iv) absence of pheochromocytoma/myocarditis. Exceptions included coexisting CAD in whom the 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 centers 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 cardiovascular and cerebrovascular events (MACCE: a composite of all cause death, TTS recurrence, stroke or transient ischemic 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 ± standard deviation (SD) 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 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 SupplementaryTable 1 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 polytomus 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 rule[21] was used to get pooled propensity score adjusted HR estimates and confidence intervals for each endpoint (primary and secondary), according to each of the three methods described below: stratification, and 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 stabilised 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 stabilised 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 curves[27] (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 females. 989 (65.8%) patients had hypertension, 221 (14.7%) diabetes mellitus, and 480 (32.0%) hypercholesterolemia. 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%). Patients' characteristics of the total 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 years death for patients in aspirin and no difference for the other endpoints.

### Adjusted comparison using PS with the stratification method

According to 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: PS covariate adjustment and PS IPTW method

PS 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 shows some weak association. The survival analysis for MACCE and death based on IPTW results confirmed these findings as reported 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 5 imputed datasets) within each treatment group on the true and the pseudo populations (see Supplementary Figure 2). After the application of the IPTW method, the distribution of PS between the two groups looks more symmetrical: treated PSs are “shifted” towards 0, while untreated PSs towards 1. The difference of 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- nor long-term prognosis in a large population of TTS patients. Incidence of MACCE in patients discharged with aspirin, who were not randomized but were adjusted for a higher burden of comorbidities 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.

TTS 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-inhibitors 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. a beneficial effect of aspirin on an in-hospital combined endpoint has been reported when given on TTS index event.[18] However, this effect may result from the combined therapy of aspirin and clopidogrel together. Moreover, the authors evaluated only hospital events in a relatively low sample size, which may have produced incidental findings.

In line with our results, Fazio et al. demonstrated a lack of benefit of in-hospital aspirin administration on both hospitalisation length and ejection fraction improvement in a relatively small number of TTS patients.[38] 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 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 hospitalisation once the clinical picture of TTS has been unmasked, unless there are coexisting comorbidities 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 the standardized differences before and after propensity score using IPTW on the covariates used, with satisfactory results (Supplementary Table 2): in fact, the computation of standardized differences (SD) demonstrate that even though some of the 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 do not show any particular non-linear relationships (see supplementary Figure 1). Moreover, in the stratification analysis, we used 3 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 the present is the largest available registry on this topic. This is particularly true for MI, which occurred only for 9 patients leading to large CI after PS adjustement.

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

**CONCLUSIONS**

In the present analysis, we found no evidence, after adjusting for potential confounding factors, 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.

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## FIGURE LEGENDS

**Figure 1.** Study design.

MACCE denotes major adverse cardiac and cerebrovascular event; TIA transient ischemic attack, TTS takotsubo syndrome.

**Figure 2.** Inverse probability of treatment weighting adjusted Kaplan-Meier Analysis.

Colored bands represent the 95% pointwise confidence bands.

MACCE denotes major adverse cardiac and cerebrovascular event; IPTW, inverse probability of treatment weighting.