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

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# 1 Impact of Aspirin on Takotsubo Syndrome: A Propensity Score Based 2 Analysis of the InterTAK Registry

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**Running title:** Aspirin in Takotsubo syndrome

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## 1 **ABSTRACT**

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

4 **Methods and Results:** Patients from the International Takotsubo Registry (InterTAK Registry)  
5 were categorized into two groups based on aspirin prescription at discharge. A comparison of  
6 clinical outcomes between the two groups was performed using an adjusted analysis with  
7 propensity score stratification; results from the unadjusted analysis were also reported to note the  
8 effect of the PS adjustment. Major adverse cardiac and cerebrovascular events (MACCE: a  
9 composite of death, myocardial infarction, TTS recurrence, stroke or transient ischemic attack  
10 [TIA]) were assessed at 30-day and 5-year follow-up. A total of 1533 TTS patients with known  
11 status regarding aspirin prescription at discharge were included. According to the adjusted analysis  
12 based on PS stratification, aspirin was not associated with a lower hazard of MACCE at 30-day  
13 (Hazard ratio [HR] 1.24, 95% confidence interval [CI] 0.50-3.04, P=0.64) or 5-year follow-up (HR  
14 1.11, 95% CI 0.78-1.58, P=0.58). These results were confirmed by sensitivity analyses performed  
15 with alternative PS based methods, i.e. covariate adjustment and inverse probability of treatment  
16 weighting.

17 **Conclusion:** In the present study, no association was found between aspirin use in TTS patients  
18 and a reduced risk of MACCE at 30-day and 5-year follow-up. These findings should be confirmed  
19 in adequately powered randomized controlled trials. (ClinicalTrials.gov number: NCT01947621)

20

21 **Keywords:** Takotsubo syndrome; acute heart failure; outcome; medical therapy; aspirin

## 1 INTRODUCTION

2 Takotsubo syndrome (TTS) mostly affects postmenopausal women and is usually preceded  
3 by an emotional or physical trigger.<sup>1-3</sup> Clinical symptoms and signs at presentation, along with  
4 electrocardiographic (ECG) and laboratory changes, may mimic acute coronary syndrome (ACS)  
5 or acute heart failure.<sup>1, 4-6</sup> Although TTS has long been considered a benign condition, recent  
6 studies reported that it can be associated with significant adverse events both during  
7 hospitalization and after discharge.<sup>1, 7-12</sup> Therefore, there is a compelling need for an optimal  
8 preventive therapy to reduce the incidence of adverse events following TTS. According to recent  
9 data, angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers have been  
10 reported to reduce mortality<sup>1</sup> and recurrence of TTS,<sup>13</sup> while beta-blockers have not shown  
11 beneficial effects.<sup>1, 14</sup> However, data on therapeutic management of TTS are mainly based on small  
12 case series,<sup>15</sup> meta-analyses,<sup>13, 16</sup> or retrospective data. There is still a lack of knowledge available  
13 on optimal treatment strategies.

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

## 1 METHODS

### 2 Data collection

3 The InterTAK Registry is an observational, prospective, and retrospective registry  
4 established at the University Hospital Zurich in 2011 in collaboration with 25 cardiovascular centers  
5 across 9 countries.<sup>1, 3</sup> Patients were included in the registry between 2011 and 2014 based on  
6 modified Mayo Clinic Diagnostic Criteria as previously reported:<sup>1, 19</sup> i) transient abnormality of left  
7 ventricular wall-motion extending beyond a single coronary artery perfusion territory, ii) absence of  
8 obstructive coronary artery disease (CAD) or evidence of acute plaque rupture, iii) presence of new  
9 electrocardiographic abnormalities or elevation in troponin and iv) absence of  
10 pheochromocytoma/myocarditis. Exceptions included coexisting CAD in whom the wall motion  
11 abnormality was congruent with a single coronary artery territory or death during the acute phase  
12 before documentation of wall motion recovery. Data on demographics, triggering factors,  
13 cardiovascular risk factors, haemodynamic and angiographic findings, ECG and echocardiography  
14 parameters, laboratory values, use of medications, in-hospital complications, and management  
15 were collected through standardized forms on admission or during revision of clinical charts.

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

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

24

### 25 Study outcomes

26 Follow-up data were collected from clinical visits, medical charts, or telephone interviews as  
27 previously described.<sup>1</sup> The incidence of major adverse cardiovascular and cerebrovascular events  
28 (MACCE: a composite of all cause death, TTS recurrence, stroke or transient ischemic attack

1[TIA], or myocardial infarction [MI]) at 30-day and 5-year follow-up were the co-primary outcomes  
2in the present analysis. Additionally, single components of MACCE at 5-year follow-up were  
3analysed.

4

## 5Statistical analysis

6In the unadjusted analysis, continuous variables were summarized as mean  $\pm$  standard deviation  
7(SD) or median (1st-3rd quartile), and frequencies of categorical variables are presented as  
8numbers with percentages. Categorical variables were compared with the Pearson chi-square test,  
9continuous variables with the Student t-test.

10An adjusted analysis based on propensity score (PS) was performed. PS is the probability that  
11each individual patient is included in the treatment group and is usually estimated via logistic  
12regression based on the available baseline covariates. PS methods are used to compensate for  
13the lack of proper statistical design and randomization in observational studies, like the present  
14one. **All variables expected to be associated with the outcomes of interest, or with both  
15aspirin prescription and outcomes, are listed in SupplementaryTable 1 and were used to  
16construct the PS model.**

17The first step of the adjusted analysis was the treatment of missing data, which were present for a  
18high number of variables (69 covariates out of 136). Assuming that data were missing at random  
19and considering only the variables with less than 50% of missing data (the other covariates were  
20excluded from the analyses)<sup>20</sup>, we used polytomus logistic regression, logistic regression and  
21predictive mean matching as multiple imputation techniques to fill in missing values, using the R  
22*mice* package (version 3.6.0). We imputed five different datasets and the same statistical analyses  
23were performed on each of them. After that, Rubin's rule<sup>21</sup> was used to get pooled propensity score  
24adjusted HR estimates and confidence intervals for each endpoint (primary and secondary),  
25according to each of the three methods described below: stratification, and covariate adjustment  
26and inverse probability of treatment weighting (IPTW) as sensitivity analysis.

27With the method based on stratification, the total dataset is divided into mutually exclusive groups  
28(strata), based on quantiles (in our case, tertiles) of the estimated PS; in this way, subjects from

1 both arms are stratified in subsets that are defined by specific thresholds in PS.<sup>22, 23</sup> Then, all strata  
2 are included in a stratified proportional hazard Cox model to get an estimate of the HR for  
3 treatment, as previously described by Austin.<sup>24</sup>

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

7 Finally, the IPTW technique involves assigning to each patient a stabilised weight equal to  
8  $(1-p)/(1-PS)$  if a control, or equal to  $p/PS$  if a treated patient,<sup>20</sup> where  $p$  is the probability of  
9 treatment without any covariate and  $PS$  is the value of the PS for that patient. The choice of  
10 stabilised weights allowed us to work with a pseudo-sample (as large as the sum of the weights)  
11 that has approximately the same size as the actual one.<sup>26</sup> Then, the weights were included in the  
12 survival analysis to estimate two adjusted Kaplan-Meier curves<sup>27</sup> (one for each treatment). The  
13 weights were also used to estimate the parameters of the Cox model, and in particular the HR.<sup>28</sup>

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

16 The adjusted statistical analysis was performed using R 3.5.1 and some of its packages<sup>29,30</sup>,  
17 notably ***mice* package (version 3.6.0)**, *rms* (version 5.1-3.1) and *survival* (version 2.44-1.1).



## 1 RESULTS

### 2 Study population

3 Out of 1750 patients in the InterTAK Registry, 1533 with documented status regarding  
4 aspirin at discharge were included in the present analysis (Figure 1). The mean age was  $66.4 \pm 13.1$   
5 years and 1382 (90.2%) were females. 989 (65.8%) patients had hypertension, 221 (14.7%)  
6 diabetes mellitus, and 480 (32.0%) hypercholesterolemia. ST-segment elevation was observed in  
7 7606 (43.5%) patients on admission. An emotional trigger was identified in 447 (29.2%) patients and  
8 a physical trigger in 533 (34.8%). Patients' characteristics of the total study cohort and of TTS  
9 patients with and without aspirin at discharge are summarized in Table 1. Unadjusted outcomes  
10 are reported in Table 2, showing a higher risk of 5 years death for patients in aspirin and no  
11 difference for the other endpoints.

12

### 13 Adjusted comparison using PS with the stratification method

14 According to PS stratification method, aspirin was not associated with a reduced hazard of  
15 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  
16 0.78-1.58,  $P=0.58$ ). Furthermore, no significant differences were observed for the single  
17 components of MACCE, including death (HR 1.36, 95% CI 0.79-2.34,  $P=0.27$ ), TTS recurrence  
18 (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  
19 3.28, 95% CI 0.38-28.28,  $P=0.28$ ) (Table 2).

20

### 21 Sensitivity analysis: PS covariate adjustment and PS IPTW method

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

27 In order to verify that the application of the IPTW method allowed to achieve a gain in  
28 similarity between the active and control groups, we plotted two "mirrored" histograms showing the

1distribution of PS (averaged on 5 imputed datasets) within each treatment group on the true and  
2the pseudo populations (see Supplementary Figure 2). After the application of the IPTW method,  
3the distribution of PS between the two groups looks more symmetrical: treated PSs are “shifted”  
4towards 0, while untreated PSs towards 1. The difference of frequency within each PS interval  
5between the active and control groups is due to the different sizes of the two groups, 1031 treated  
6subjects and 502 untreated ones.

## 1 DISCUSSION

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

4 The present study found that aspirin at hospital discharge did not relate to short- nor long-  
5 term prognosis in a large population of TTS patients. Incidence of MACCE in patients discharged  
6 with aspirin, who were not randomized but were adjusted for a higher burden of comorbidities with  
7 PS methods, was not significantly different compared to patients without aspirin, both at short and  
8 long-term follow-up. Furthermore, single components of MACCE were similar at 5 years. Presence  
9 of CAD at baseline did not affect these results.

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

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

1 In line with our results, Fazio et al. demonstrated a lack of benefit of in-hospital aspirin  
2 administration on both hospitalisation length and ejection fraction improvement in a relatively small  
3 number of TTS patients.<sup>38</sup> Of note, we focused on aspirin use after hospital discharge, also  
4 adjusting for major confounding factors with PS-stratified analysis, and similarly we could not  
5 demonstrate an association between aspirin and improved outcome at follow-up. We found some  
6 evidence of weak association between aspirin and only TTS recurrence; such weak association is  
7 detected by the covariate adjustment and the IPTW methods and not by the stratification method.  
8 Therefore, this potential association should be interpreted carefully, considering the lack of a  
9 supporting pathophysiological mechanism. Since any potential benefit should be pondered with the  
10 inevitable higher bleeding risk in patients taking aspirin on a long-term basis, the routine use of  
11 aspirin should not be encouraged especially in patients at high risk for bleeding.<sup>39</sup>

12 Our results suggest that TTS *per se* does not represent an indication for treatment with  
13 aspirin. Aspirin treatment might be withdrawn even during hospitalisation once the clinical picture  
14 of TTS has been unmasked, unless there are coexisting comorbidities that confer a high  
15 atherosclerotic risk and require antiplatelet therapy according to current guidelines.

16

### 17 **Study limitations**

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

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

1 Performance of PS was tested by assessing the standardized differences before and after  
2 propensity score using IPTW on the covariates used, with satisfactory results (Supplementary  
3 Table 2): in fact, the computation of standardized differences (SD) demonstrate that even though  
4 some of the SDs increased from the unadjusted to the adjusted population, this led to an overall  
5 decrease in all SDs adjusted with IPTW, so that almost all variables have a SD lower than 0.1  
6 between treatment groups. Regarding non linearity, residuals are symmetrically distributed around  
7 0 and lowess interpolation within each plot do not show any particular non-linear relationships (see  
8 supplementary Figure 1). Moreover, in the stratification analysis, we used 3 strata, with a potential  
9 higher risk of bias: however, the results are consistent with the other two analyses, confirming the  
10 overall strength of our model.

11 Proper sample size calculation showed that this study is formally underpowered for main  
12 outcomes, although it should be remembered that the present is the largest available registry on  
13 this topic. This is particularly true for MI, which occurred only for 9 patients leading to large CI after  
14 PS adjustment.

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

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## 20 **CONCLUSIONS**

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

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## 1 **FIGURE LEGENDS**

2 **Figure 1.** Study design.

3 MACCE denotes major adverse cardiac and cerebrovascular event; TIA transient ischemic attack,

4 TTS takotsubo syndrome.

5

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

7 Colored bands represent the 95% pointwise confidence bands.

8 MACCE denotes major adverse cardiac and cerebrovascular event; IPTW, inverse probability of

9 treatment weighting.

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