





Impact of intra-aortic balloon counterpulsation on all-cause mortality among patients with Takotsubo syndrome complicated by cardiogenic shock: results from the German-Italian-Spanish (GEIST) registry

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Received 31 March 2022; revised 15 December 2022; accepted 20 January 2023; online publish-ahead-of-print 24 January 2023

Handling Editor: Davide Stolfo

Aims

Takotsubo syndrome (TTS) is an acute and reversible left ventricular dysfunction and can be complicated by cardiogenic shock (CS). However, few data are available on optimal care in TTS complicated by CS. Aim of this study was to evaluate short- and long-term impact of intra-aortic balloon pumping (IABP) on mortality in this setting.

Methods and results

In a multi-centre, international registry on TTS, 2248 consecutive patients were enrolled from 38 centres from Germany, Italy, and Spain. Of the 2248 patients, 212 (9.4%) experienced CS. Patients with CS had a higher prevalence of diabetes (27% vs. 19%), male sex (25% vs. 10%), and right ventricular involvement (10% vs. 5%) ($P < 0.01$ in all cases). Forty-three patients with CS (20% of 212) received IABP within 8 h (interquartile range 4–18) after admission. No differences in terms of age,

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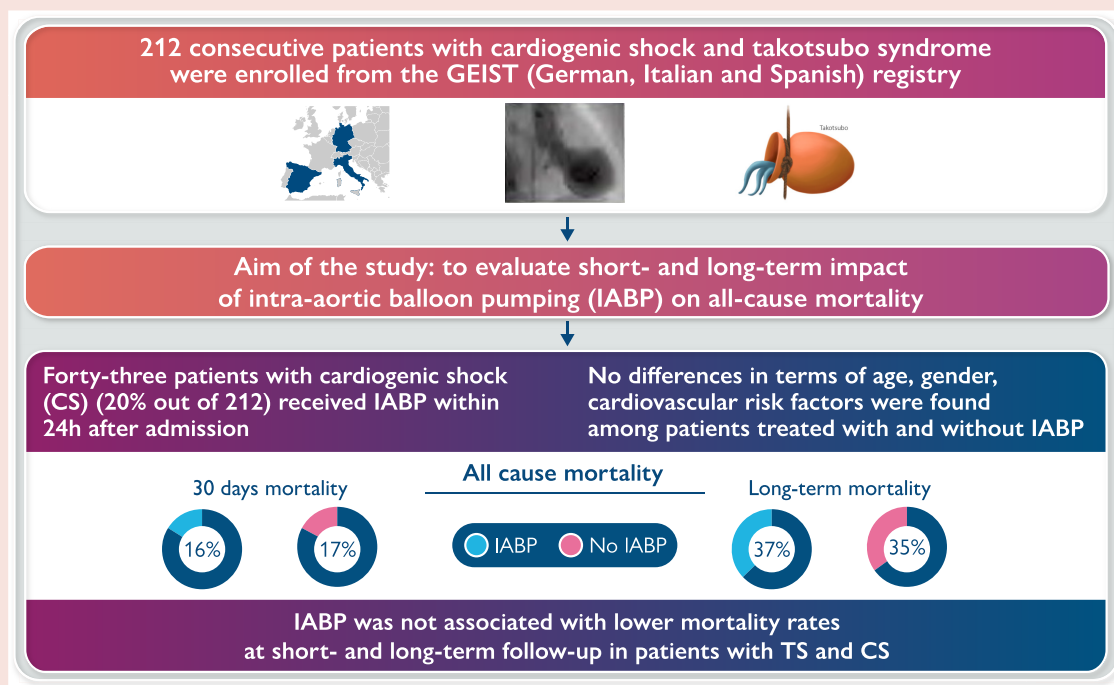
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gender, cardiovascular risk factors, and admission left ventricular ejection fraction were found among patients with and without IABP. There were no significant differences in terms of 30-day mortality (16% vs. 17%, $P = 0.98$), length of hospitalization (18.9 vs. 16.7 days, $P = 0.51$), and need of invasive ventilation (35% vs. 41%, $P = 0.60$) among two groups: 30-day survival was not significantly different even after propensity score adjustment (log-rank $P = 0.73$). At 42-month follow-up, overall mortality in patients with CS and TTS was 35%, not significantly different between patients receiving IABP and not (37% vs. 35%, $P = 0.72$).

Conclusions

In a large multi-centre observational registry, the use of IABP was not associated with lower mortality rates at short- and long-term follow-up in patients with TTS and CS.

Graphical Abstract



Mechanical support with intra-aortic balloon pumping (IABP) in patients with Takotsubo syndrome and cardiogenic shock was not associated with survival benefit at short- and long-term mortality.

Keywords

Cardiogenic shock • GEIST • IABP • In-hospital complications • Intra-aortic balloon counter-pulsation • Stress cardiomyopathy • Takotsubo syndrome

Introduction

Takotsubo syndrome (TTS) is a reversible and transient left ventricular (LV) dysfunction,¹ featured by acute heart failure. Although considered as a benign disease, several studies showed that TTS is featured by high rates of in-hospital complications and not favourable long-term outcome.^{2,3} The incidence of in-hospital complications (IHCs) is about 25%,⁴ and these IHCs are mainly represented by several forms of acute heart failure including pulmonary oedema and cardiogenic shock (CS).^{5,6} Incidence of CS in patients admitted with TTS ranges from 9.5% to 11.4%^{7,8,9} and has been associated with poor outcome at short- and long-term follow-up. However, there is no standard therapy for CS in TTS. Several approaches have currently been proposed as mechanical support mainly with intra-aortic balloon counterpulsation

(IABP),¹⁰ levosimendan,¹¹ catecholamine infusion,¹² and short-acting β 1-selective blocker (esmolol)¹³ in case of LV outflow tract obstruction.

Mechanical support with IABP in case of CS may be potentially useful by reduction of afterload in left ventricular systole and increase of coronary blood flow during diastole.

However, the role of IABP in CS is still debated. Although for patients with acute myocardial infarction and CS, IABP has no effect on all-cause mortality,¹⁴ in the context of acute-on-chronic heart failure complicated by cardiogenic shock IABP can provide potential benefit to those patient candidates for cardiac replacement therapies.¹⁵

Aim of this study was therefore to assess short- and long-term outcome in patients with CS and TTS treated with IABP in a large, international, multi-centre registry.

Methods

Study population

The study population included 212 consecutive patients with CS and TTS from a multi-centre-international registry (German, Italian, and Spanish Takotsubo registry, NCT 04361994) that has enrolled 2248 patients, involving 38 institutions from Germany, Italy, and Spain (Figure 1; Supplementary material online, Table S1).

Inclusion criteria

All patients with suspected diagnosis of TTS underwent coronary angiogram. The diagnosis of TTS was based on the position statement of the 2016 European Heart Failure Association.¹⁶

Clinical and echocardiographic examination

All patients underwent clinical examination, and baseline features like gender, age, medical history, and kind of stressors were recorded. All patients underwent two-dimensional Doppler echocardiogram examination at admission. The LV ejection fraction (LVEF) was calculated through the Simpson method using the two- and four-chamber view.¹⁷ LV dysfunction patterns were classified as previously defined: apical ballooning, mid-ventricular ballooning, and basal ballooning.¹⁸

Cardiogenic shock management

Patients received the best available medical treatment according to current guidelines for CS.¹⁹ Catecholaminergic inotropic agents were avoided, and fluid administration was performed according to echocardiographic evaluation of mitral and aortic valve and RV function.²⁰ According to operator choice, patients with CS underwent IABP implantation or not. The IABP was inserted within 8 h (interquartile range 4–18) after admission either before or immediately after coronary angiography, with the timing of the insertion at the discretion of the investigator. Support was initiated with the use of 1:1 ECG triggering (i.e. balloon inflation and deflation triggered by the R wave) and was maintained until there was sustained haemodynamic stabilization, defined as a systolic values of blood pressure higher than 90 mmHg for more than 30 min. Weaning from the pump was achieved through reduction of the trigger ratio.²¹ No additional cardiac assistance device, other than IABP, was used for patients enrolled in this registry.

Heart failure management

All patients received standard therapy for acute heart failure mainly with diuretics and ventilatory support according to current guidelines.²² No differences in terms of heart failure therapy were found over time and among centres.

Definition of outcome

The primary clinical endpoint was all cause mortality at 30 days and at long-term among patients with CS and TTS treated with mechanical support with IABP or not.

Definition of CS was as follows: systolic blood pressure less than 90 mmHg for more than 30 min and clinical signs of impaired organ perfusion and pulmonary congestion, with one of the following criteria: (i) cold skin and extremities; (ii) altered mental status; (iii) level of arterial lactate >2 mmol/L; or (iv) oliguria (≤ 30 mL per hour).²³

All patients gave a written informed consent for participation in the registry. The study received approval by an institutional review board and ethics committee in each centre (approval number 143/2019 of the ethics committee for the coordinating centre).

Statistical analysis

Continuous variables were reported as mean \pm standard deviation (SD), and categorical variables were expressed as proportions; the Kolmogorov–Smirnov test was used to evaluate normal distribution of variables. Groups were compared with unpaired *t*-test or χ^2 test as required. Log-rank test and Kaplan–Meier plots were used to evaluate events survival freedom at short- and long-term follow-up.

Cox's regression analysis was used to identify predictors for mortality; relative risks (RRs) with 95% confidence intervals were calculated. Forward multivariable logistic regression analysis was used for correcting bias of principal confounders. Variables significant at univariate analysis ($P < 0.05$) were included in multivariate analysis.

A propensity-matched population was selected from overall population with CS after calculation of a propensity score for receiving IABP according to the following variables: age, gender, and LVEF. A nearest-neighbor 1:1 variable ratio, parallel, balanced propensity-matching model without replacement was made using caliper of width equal to 0.001 propensity score discordance. A *P*-value <0.05 was considered as statistically significant.

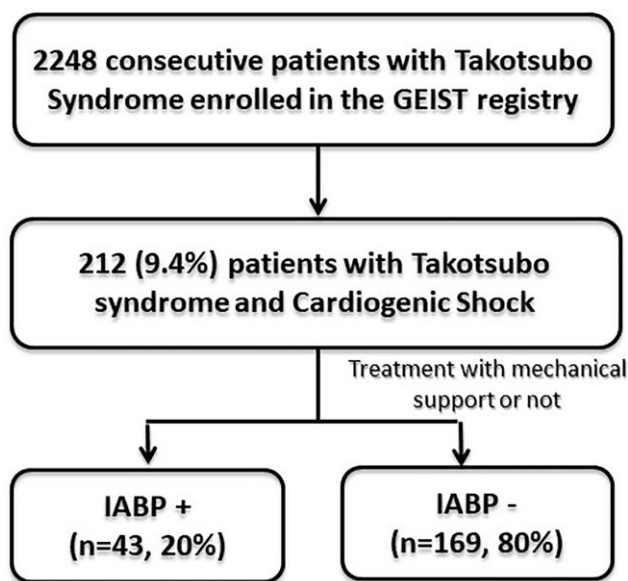


Figure 1 Flow chart of patient's enrolment.

Results

Clinical features of cardiogenic shock in Takotsubo syndrome

CS was observed in 212 (9.4%) of 2248 patients. Mean age of patients with CS was 71 ± 13 years, and one fourth ($n = 53$) were male. A stressor trigger was identified in about three-fourths of patients (74%) with similar rate of emotional and physical triggers (38% and 36%, respectively). Admission LVEF was $35 \pm 9\%$, and apical ballooning was the predominant contraction pattern (82%). Mean hospital stay was 16 ± 10 days and in-hospital mortality 16%.

Additional in-hospital complications were as follows: need of invasive ventilation 39% ($n = 84$), need of mechanical cardiac support with intra-aortic balloon pump 20% ($n = 43$), need of inotropic drugs 21% ($n = 44$), ventricular arrhythmias 6% ($n = 13$), stroke 1.8% ($n = 4$), and LV thrombi 1.8% ($n = 4$).

When comparing patients with and without CS. Patients with CS had a higher prevalence of diabetes (27% vs. 19%, $P < 0.01$), previous neurological disorders (21% vs. 14%, $P < 0.01$), male sex (25% vs.

10%, $P < 0.01$), lower LVEF ($35 \pm 9\%$ vs. $40 \pm 12\%$, $P < 0.01$), and right ventricular involvement (10% vs. 5%, $P < 0.01$) (see [Supplementary material online, Table S1](#)).

Intra-aortic balloon pump use in cardiogenic shock

According to operator choice, 43 patients of 212 (20%) with CS received IABP. No significant differences in terms of age, gender, cardiovascular risk factors, and admission LVEF were found among patients with and without IABP ([Table 1](#)). Moreover, between two groups, there were no differences in terms of 30-day mortality (16.2% vs. 17%, $P = 0.98$), length of hospitalization (16 ± 12 vs. 17 ± 9 , $P = 0.62$), and need of invasive ventilation (35% vs. 41%, $P = 0.60$) ([Table 2](#)): 30-day survival was not significantly different even at propensity matching analysis (log-rank $P = 0.735$) ([Figure 2](#); [Supplementary material online, Table S2](#)).

Long-term follow-up

At 42-month follow-up, overall-mortality was 35% in patients with CS and TTS and did not differ between patients receiving IABP and not (37% vs. 35%, $P = 0.72$). At multivariate analysis including age, male gender, use of IABP, and LVEF, age and male sex were found as independent predictors of mortality (RR 1.03, 95% CI 1.04–1.06, $P = 0.01$, RR 1.8, 95% CI 1.09–3.2, $P = 0.02$, respectively) ([Table 3](#)).

Discussion

This study evaluates, in a large multi-centre international registry, the prognostic impact of mechanical support with IABP in patients with TTS and CS ([Graphical Abstract](#)). We found that the incidence of CS in the present cohort was 9.4%. Mechanical support with IABP did not impact on overall mortality at short and long-term follow-up among TTS patients with CS.

CS is a potential IHC in patients admitted for TTS, with an incidence of 9.4–11.4%.^{7,8} Moreover, TTS patients may experience cardiac arrest and need of cardiopulmonary resuscitation with an incidence of 4.9–5%.^{24,25} CS in TTS has been associated with higher mortality rates at short- and long-term follow-up; therefore, an optimal management is crucial.^{6,7,26}

In this setting, support with inotropes should be avoided given their potential role in pathogenesis of TTS. Catecholamines could induce depression of cardiomyocytes mainly on β_2 adrenergic receptors that can be mainly found on apical LV segments.²⁷ Indeed, in a study by Ansari

Table 1 Baseline clinical, echocardiographic and laboratory features of patients with Takotsubo syndrome and cardiogenic shock, treated with intra-aortic balloon pump or not

	Cardiogenic shock $n = 212$ Mean	IABP $n = 43$ Mean	No IABP $n = 169$ Mean	P value
Age, years	71 ± 13	72 ± 10	70 ± 13	0.41
Male sex	25%	23%	26%	0.41
Hypertension	75%	81%	71%	0.17
Diabetes	27%	29%	23%	0.44
Dyslipidemia	39%	33%	44%	0.20
Smoke	16%	10%	17%	0.25
Neurological disorder	15%	13%	19%	0.33
Emotional stress	38%	23%	39%	0.06
Physical stress	36%	44%	34%	0.23
Hospital stay, days	16 ± 10	16 ± 12	17 ± 9	0.62
Admission LVEF, %	$35 \pm 9\%$	$36 \pm 9\%$	$35 \pm 8\%$	0.72
RV involvement	5%	7%	5%	0.56
LVOTO	7%	2%	8%	0.28
Apical ballooning	82%	86%	90%	0.69
Mid ballooning	16%	14%	8%	0.77
Basal ballooning	2%	0%	2%	0.62
ECG features at admission				
ST elevation	39%	47%	38%	0.30
Long QT	30%	29%	31%	0.79
Negative T waves	50%	49%	51%	0.80

LVEF, left ventricular ejection fraction; LVOTO, left ventricular outflow tract obstruction, RV, right ventricular.

Over 212 subjects with Takotsubo syndrome and cardiogenic shock, we had no missing data for age, gender, ballooning type, 3.3–3.7% of missing data for cardiovascular risk factors, 2–12% for comorbidities, 1.4–1.9% for symptoms, 2.4% for LVEF, 10–12% for echo features, 2.3–10–4% for ECG features, and 20% for troponin levels.

Table 2 In-hospital complications in patients with cardiogenic shock treated with intra-aortic balloon pumping and not

	IABP ($n = 43$)	NO IABP ($n = 169$)	P value
Invasive ventilation during hospitalization	35% ($n = 15$)	41% ($n = 69$)	0.60
Stroke	4% ($n = 2$)	1% ($n = 2$)	0.13
Left ventricular thrombus	2% ($n = 1$)	2% ($n = 3$)	0.81
Ventricular arrhythmias	4.6% ($n = 2$)	6.5% ($n = 11$)	0.88
Catecholamine infusion	11% ($n = 5$)	23% ($n = 39$)	0.14
In-hospital death	11% ($n = 5$)	17% ($n = 29$)	0.14
Length of hospitalization (mean days)	16 ± 12	17 ± 9	0.62

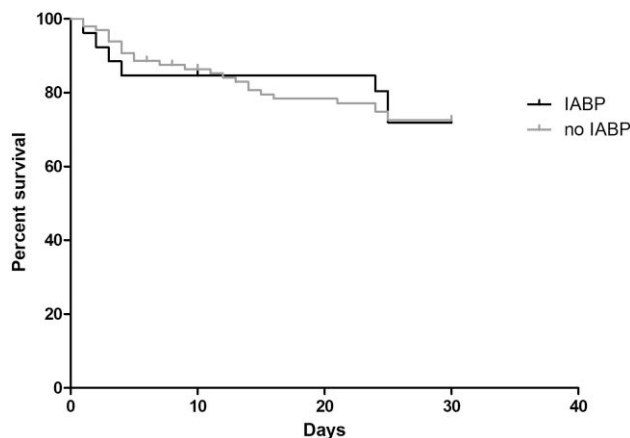


Figure 2 Kaplan–Meier curves with overall survival in patients treated with intra-aortic balloon pump at 30-day follow-up and not. No differences were found between patients receiving intra-aortic balloon pump and not (log-rank $P=0.73$).

Table 3 Multivariable analysis of independent predictors of mortality at long-term among Takotsubo syndrome patients

	Multivariable analysis RR (95% CI)	P value
Age, years	1.03 (1.01–1.06)	0.01
Male sex	1.88 (1.09–3.24)	0.02
Intra-aortic balloon pump	0.75 (0.43–1.33)	0.33
Admission LVEF, %	4.79 (0.28–80.916)	0.27

LVEF, left ventricular ejection fraction.

*et al.*¹² comparing TTS patients treated with and without catecholamine support, 30-day mortality (51.4% vs. 17.2%, $P < 0.01$) as long-term mortality (80.9% vs. 38.7%, $P < 0.01$) was significantly higher in the first group. Other pharmacological options are the use of intravenous levosimendan¹¹ or short-acting β_1 selective blockers (esmolol)¹³ in case of LV outflow tract obstruction.

Mechanical circulatory support could represent an option in patients with TTS and CS and can be used as a bridge-to-recovery strategy. TTS haemodynamics are featured by severely increased filling pressures in the absence of shock, probably due to stunning-related impairment of myocardial compliance and relaxation. Currently, there are three different percutaneous support systems mainly used: IABP, extracorporeal membrane oxygenation (ECMO), and microaxial pumps (i.e. Impella™, Abiomed).

IABP reduces afterload in systole, increasing coronary blood flow during diastole. IABP could be harmful in patients with TTS, as deflation of the IABP during systole may increase the transaortic gradient²⁸ and thereby induce or aggravate LV outflow tract obstruction.²⁹ If used, it is mandatory to evaluate LV outflow tract before IABP implantation through echocardiogram. Few data have been published on IABP and TTS, and only some case report evaluated the use of IABP in TTS with CS^{30,31} and after resuscitation.³²

Veno-arterial ECMO drains blood from the right atrium and provides oxygenated blood to the lower tract of the abdominal aorta.³³ ECMO is a potential therapeutic strategy during right ventricular failure; the procedure inducing right-to-left shunt reduces preload and

increases organ perfusion enhancing afterload. However, this may have some several side effects as worsening mitral regurgitation and pulmonary oedema during outflow tract obstruction. According to the current literature, ECMO has been used in patients with TTS and CS³⁴ or in refractory arrest.³⁵

Micro-axial pumps as Impella drain blood from the LV and expel it to the aorta, providing antegrade blood flow. It drains blood during systole and diastole unloading the LV and contributes to myocardial recovery. Impella bridges LV outflow tract obstruction and is a therapeutic option for those cases where CS is complicated by LV outflow obstruction.³⁶ Currently, only a case series of 16 patients evaluated the safety and efficacy of Impella with potential benefit in term of in-hospital mortality.³⁷

Although in several case report the use of mechanical support in TTS appears to be safe as a bridge to myocardial recovery, there are no data on long-term outcome. The present study reports the impact of IABP on survival in TTS patients with CS. According to the present study, IABP has no impact on mortality at short- and long-term follow-up. In the present study, in-hospital mortality was not affected in patients treated or not with IABP (11% vs. 17%, $P = 0.14$). This trend was also observed at 30-day follow-up, with similar mortality between patient treated with IABP and not (16.2% vs. 17%, $P = 0.98$).

These data reflect previous randomized studies that evaluated mechanical support in myocardial infarction and CS. Thiele *et al.*³⁸ found in a randomized open-label trial that IABP has no impact on survival among patients with CS and myocardial infarction at short- and long-term.

Moreover, recently Miller *et al.*³⁹ in a propensity-matched analysis of patients with acute myocardial infarction complicated by CS found that mechanical circulatory support with IMPELLA was associated with increased short-term and 1-year risk of mortality, bleeding, and cost compared with IABP. Therefore, the use of mechanical support in the context of CS is still debated, and a tailored approach is needed.

According to our data, IABP cannot be generally recommended in TTS patients with CS. The main reason for the missing effect of IABP on mortality in TTS might be the fact that mortality in TTS is mainly driven by non-cardiovascular comorbidities.^{40,41} Randomized trials are needed in this context to evaluate the best pharmacological treatment to improve survival in TTS patients with CS.

Limitations

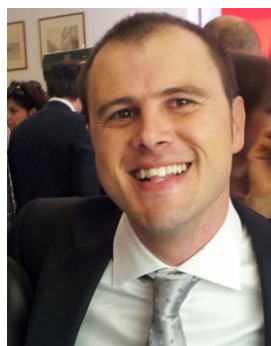
The German Italian Spanish Takotsubo registry is a multi-centre observational registry in which data were collected from several different

institutions. This is not a randomized trial, and use of IABP was left at operator choice. Although data were prospectively collected, analysis was performed retrospectively. The study has no control group for patients with CS. Due to the small sample size of patients with TTS and CS, even after several statistical analysis as logistic regression and propensity score matching, a residual bias cannot be completely excluded. The final sample of patients with CS may be not powered enough to detect a significant difference in terms of mortality. Kind of vasopressor and dosages were not prospectively recorded. Troponin and BNP values were collected with different unit of measures and therefore were not reported in the present study. Weaning from mechanical circulatory support was performed when systolic blood pressure was higher than 90 mmHg for >30 min; however, a multiparametric approach could be considered.⁴²

Conclusions

In a large multi-centre observational registry, the use of IABP was not associated with lower mortality rates at short- and long-term follow-up in patients with TTS and CS.

Lead author biography



Francesco Santoro, MD, PhD, is cardiologist at the University hospital of Foggia, Policlinico Riuniti, Italy. In 2013, he completed his training at Texas Arrhythmia Institute, Austin, TX, USA, under the supervision of Dr. Andrea Natale, and, in 2015–18, at electrophysiology laboratory at the Department of Cardiology, Asklepios Klinik St. Georg, Hamburg, Germany. His research fields include: Cardiomyopathies (Takotsubo syndrome) and catheter ablation of atrial fibrillation and ventricular tachycardia.

He authored 180 publications in indexed journals, about 175 abstracts and 6 electrophysiology book chapters.

Data availability

Data would be available on reasonable request to the corresponding author.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

Acknowledgements

We are greatly indebted to all collaborators of the GEIST registry.

Funding

None declared.

Conflict of interest: None declared.

References

1. Dias A, Núñez Gil IJ, Santoro F, Madias JE, Pelliccia F, Brunetti ND, Salmoirago-Blotcher E, Sharkey SW, Eitel I, Akashi YJ, El-Battrawy I, Franco E, Akin I, Jaguszewski M, Dawson D, Figueredo VM, Napp LC, Christensen TE, Hebert K, Ben-Dor I, Ozaki Y, García-García HM, Kajita AH, Akasaka T, Kurisu S, Lerman A, Waksman R.

- Takotsubo syndrome: state-of-the-art review by an expert panel—part 1. *Cardiovasc Revasc Med* 2019;**20**:70–79.
2. Stiermaier T, Moeller C, Oehler K, Desch S, Graf T, Eitel C, Vonthein R, Schuler G, Thiele H, Eitel I. Long-term excess mortality in Takotsubo cardiomyopathy: predictors, causes and clinical consequences. *Eur J Heart Fail* 2016;**18**:650–656.
3. Santoro F, Stiermaier T, Tarantino N, Guastafierro F, Graf T, Möller C, Di Martino LFM, Thiele H, Di Biase M, Eitel I, Brunetti ND. Impact of persistent ST elevation on outcome in patients with Takotsubo syndrome. Results from the German Italian stress cardiomyopathy (GEIST) registry. *Int J Cardiol* 2018;**255**:140–144.
4. 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, Tschöpe C, Schultheiss HP, Laney CA, Rajan L, Michels G, Pfister R, Ukena C, Böhm 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, Lüscher TF. Clinical features and outcomes of Takotsubo (stress) cardiomyopathy. *N Engl J Med* 2015;**373**:929–938.
5. Madhavan M, Rihal CS, Lerman A, Prasad A. Acute heart failure in apical ballooning syndrome (Takotsubo/stress cardiomyopathy): clinical correlates and mayo clinic risk score. *J Am Coll Cardiol* 2011;**57**:1400–1401.
6. Santoro F, Núñez Gil IJ, Stiermaier T, El-Battrawy I, Guerra F, Novo G, Guastafierro F, Tarantino N, Novo S, Mariano E, Romeo F, Romeo F, Capucci A, Bahlmann E, Zingaro M, Cannone M, Caldarola P, Marchetti MF, Montisci R, Meloni L, Thiele H, Di Biase M, Almindro-Delia M, Sionis A, Akin I, Eitel I, Brunetti ND. Assessment of the German and Italian stress cardiomyopathy score for risk stratification for in-hospital complications in patients with Takotsubo syndrome. *JAMA Cardiol* 2019;**4**:892–899.
7. 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, Münzel T, Knorr M, Heiner S, Katus HA, Burgdorf C, Schunkert H, Thiele H, Bauersachs J, Tschöpe 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, Borggreffe M, Gilyarova E, Shilova A, Gilyarov M, Horowitz J, Kozel M, Tousek P, Widimský P, Winchester DE, Ukena C, Di Mario C, Prasad A, Böhm M, Bax JJ, Lüscher TF, Ruschitzka F, Ghadri JR, Templin C. Outcomes associated with cardiogenic shock in Takotsubo syndrome. *Circulation* 2019;**139**:413–415.
8. Almindro-Delia M, Núñez-Gil IJ, Lobo M, Andrés M, Vedia O, Sionis A, Martín-García A, Cruz Aguilera M, Pereyra E, Martín de Miguel I, Linares Vicente JA, Corbi-Pascual M, Bosch X, Fabregat Andrés O, Sánchez Grande Flecha A, Pérez-Castellanos A, Pais JL, De Mora Martín M, Escudier Villa JM, Martín Asenjo R, Guillen Marzo M, Rueda Sobella F, Aceña Á, García Acuña JM, García-Rubira JC; RETAKO Investigators. Short- and long-term prognostic relevance of cardiogenic shock in Takotsubo syndrome: results from the RETAKO registry. *JACC Heart Fail* 2018;**6**:928–936.
9. Stiermaier T, Santoro F, Eitel C, Graf T, Möller C, Tarantino N, Guastafierro F, Di Biase M, Thiele H, Brunetti ND, Eitel I. Prevalence and prognostic relevance of atrial fibrillation in patients with Takotsubo syndrome. *Int J Cardiol* 2017;**245**:156–161.
10. Nagao T, Ohwada T, Hashimoto M, Aoki K, Shimizu H, Katayama M. Intra-aortic balloon pumping is effective for hemodynamic management of catecholamine resistant ampulla (Takotsubo) cardiomyopathy. *Masui* 2004;**53**:799–802.
11. 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.
12. Ansari U, El-Battrawy I, Fastner C, Behnes M, Sattler K, Huseynov A, Baumann S, Tülümen E, Borggreffe M, Akin I. Clinical outcomes associated with catecholamine use in patients diagnosed with Takotsubo cardiomyopathy. *BMC Cardiovasc Disord* 2018;**18**:54.
13. Santoro F, Ieva R, Ferraretti A, Fanelli M, Musaico F, Tarantino N, Martino LD, Gennaro LD, Caldarola P, Biase MD, Brunetti ND. Hemodynamic effects, safety, and feasibility of intravenous esmolol infusion during Takotsubo cardiomyopathy with left ventricular outflow tract obstruction: results from a multicenter registry. *Cardiovasc Ther* 2016;**34**:161–166.
14. Thiele H, Zeymer U, Thelemann N, Neumann FJ, Hausleiter J, Abdel-Wahab M, Meyer-Saraei R, Fuernau G, Eitel I, Hambrecht R, Böhm M, Werdan K, Felix SB, Hennersdorf M, Schneider S, Quarrak T, Desch S, de Waha-Thiele S; IABP-SHOCK II Trial (Intraaortic Balloon Pump in Cardiogenic Shock II) Investigators. Intraaortic balloon pump in cardiogenic shock complicating acute myocardial infarction: long-term 6-year outcome of the randomized IABP-SHOCK II trial. *Circulation* 2019;**139**:395–403.
15. Morici N, Marini C, Sacco A, Tavazzi G, Saia F, Palazzini M, Oliva F, Ferrari GM, Colombo PC, Kapur NK, Garan AR, Pappalardo F. Intra-aortic balloon pump for acute-on-chronic heart failure complicated by cardiogenic shock. *J Card Fail* 2022;**28**:1202–1216.

16. Lyon AR, Bossone E, Schneider B, Sechtem U, Citro R, Underwood SR, Sheppard MN, Figtree GA, Parodi G, Akashi YJ, Ruschitzka F, Filippatos G, Mebazaa A, Omerovic E. Current state of knowledge on Takotsubo syndrome: a position statement from the taskforce on Takotsubo syndrome of the heart failure association of the European Society of Cardiology. *Eur J Heart Fail* 2016;**18**:8–27.
17. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise JS, Solomon SD, Spencer KT, Sutton MS, Stewart WJ; Chamber Quantification Writing Group; American Society of Echocardiography's Guidelines and Standards Committee. Recommendations for chamber quantification: a report from the American Society of Echocardiography's guidelines and standards committee and the chamber quantification writing group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. *J Am Soc Echocardiogr* 2005;**18**:1440–1463.
18. Eitel I, von Knobelsdorff-Brenkenhoff F, Bernhardt P, Carbone I, Muellerleile K, Aldrovandi A, Francone M, Desch S, Gutberlet M, Strohm O, Schuler G, Schulz-Menger J, Thiele H, Friedrich MG. Clinical characteristics and cardiovascular magnetic resonance findings in stress (Takotsubo) cardiomyopathy. *JAMA* 2011;**306**: 277–286.
19. Van Diepen S, Katz JN, Albert NM, Henry TD, Jacobs AK, Kapur NK, Kilic A, Menon V, Ohman EM, Sweitzer NK, Thiele H, Washam JB, Cohen MG. Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. *Circulation* 2017;**136**:e232–e268.
20. Santoro F, Mallardi A, Leopizzi A, Vitale E, Rawish E, Stiermaier T, Eitel I, Brunetti ND. Current knowledge and future challenges in Takotsubo syndrome: part 2-treatment and prognosis. *J Clin Med* 2021;**10**:468.
21. Thiele H, Schuler G, Neumann FJ, Hausleiter J, Olbrich HG, Schwarz B, Hennersdorf M, Empen K, Fuernau G, Desch S, de Waha S, Eitel I, Hambrecht R, Böhm M, Kurovski V, Lauer B, Minden HH, Figulla HR, Braun-Dullaeus RC, Strasser RH, Rochoch K, Maier SKG, Möllmann H, Schneider S, Ebel H, Werdan K, Zeymer U. Intraaortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock: design and rationale of the intraaortic balloon pump in cardiogenic shock II (IABP-SHOCK II) trial. *Am Heart J* 2012;**163**:938–945.
22. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P; Authors/Task Force Members; Document Reviewers. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the task force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016;**18**: 891–975.
23. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, Richardt G, Hennersdorf M, Empen K, Fuernau G, Desch S, Eitel I, Hambrecht R, Fuhrmann J, Böhm M, Ebel H, Schneider S, Schuler G, Werdan K. Intraaortic balloon support for myocardial infarction with cardiogenic shock. *N Engl J Med* 2012;**367**:1287–1296.
24. Gili S, Cammann VL, Schlossbauer SA, Kato K, D'Ascenzo F, Di Vece D, Jurisic S, Micek J, Obeid S, Bacchi B, Szawan KA, Famos F, Sarcon A, Levinson R, Ding KJ, Seifert B, Lenoir O, Bossone E, Citro R, Franke J, Napp LC, Jaguszewski M, Noutsias M, Münzel T, Knorr M, Heiner S, Katus HA, Burgdorf C, Schunkert H, Thiele H, Bauersachs J, Tschöpe 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, Gilyarova E, Shilova A, Gilyarov M, Horowitz JD, Kozel M, Tousek P, Widimský P, Winchester DE, Ukena C, Gaita F, Di Mario C, Wischnowsky MB, Bax JJ, Prasad A, Böhm M, Ruschitzka F, Lüscher TF, Ghadri JR, Templin C. Cardiac arrest in Takotsubo syndrome: results from the InterTAK registry. *Eur Heart J* 2019;**40**:2142–2151.
25. El-Battrawy I, Santoro F, Stiermaier T, Möller C, Guastafierro F, Novo G, Novo S, Santangelo A, Mariano E, Romeo F, Romeo F, Thiele H, Guerra F, Capucci A, Giannini I, Caldarola P, Brunetti ND, Eitel I, Akin I. Prevalence, management, and outcome of adverse rhythm disorders in Takotsubo syndrome: insights from the international multicenter GEIST registry. *Heart Fail Rev* 2020;**25**:505–511.
26. Dias A, Núñez Gil JJ, Santoro F, Madias JE, Pelliccia F, Brunetti ND, Salmorirago-Blotcher E, Sharkey SW, Eitel I, Akashi YJ, El-Battrawy I, Franco E, Akin I, Jaguszewski M, Dawson D, Figueredo VM, Napp LC, Christensen TE, Hebert K, Ben-Dor I, Ozaki Y, García-García HM, Kajita AH, Akasaka T, Kurisu S, Lerman A, Waksman R. Takotsubo syndrome: state-of-the-art review by an expert panel—part 2. *Cardiovasc Revasc Med* 2019;**20**:153–166.
27. Paur H, Wright PT, Sikkil MB, Tranter MH, Mansfield C, O'Gara P, Stuckey DJ, Nikolaev VO, Diakonov I, Pannell L, Gong H, Sun H, Peters NS, Petrou M, Zheng Z, Gorelik J, Lyon AR, Harding SE. High levels of circulating epinephrine trigger apical cardiodepression in a β_2 -adrenergic receptor/GI-dependent manner: a new model of Takotsubo cardiomyopathy. *Circulation* 2012;**126**:697–706.
28. Coddens J, Van Alphen J, DeLoof T, Hendrickx J. Dynamic left ventricular outflow tract obstruction caused by afterload reduction induced by intra-aortic balloon counterpulsation. *J Cardiothorac Vasc Anesth* 2002;**16**:749–751.
29. Sengen H, Imori Y, Tara S, Yamamoto T, Takano H, Shimizu W. Haemodynamic deterioration due to intra-aortic balloon counterpulsation in Takotsubo cardiomyopathy. *Eur Heart J* 2018;**39**:2118.
30. Rahal JP, Malek AM, Heilman CB. Intra-aortic balloon pump counterpulsation in aneurysmal subarachnoid hemorrhage. *World Neurosurg* 2013;**80**:e203–e207.
31. Overton T, Phillips JL, McReynolds D. Takotsubo syndrome with refractory cardiogenic shock after trauma: successful treatment with an intra-aortic balloon pump. *ANZ J Surg* 2016;**86**:202–203.
32. Bleser T, Weth C, Gorge G. Reverse Takotsubo cardiomyopathy—a life-threatening disease. Successful resuscitation of a 31-year-old woman with cardiogenic shock after a visit to the dentist. *Med Klin Intensivmed Notfmed* 2013;**108**:675–678.
33. Napp LC, Kuhn C, Hoepfer MM, Vogel-Claussen J, Haverich A, Schafer A, Bauersachs J. Cannulation strategies for percutaneous extracorporeal membrane oxygenation in adults. *Clin Res Cardiol* 2016;**105**:283–296.
34. Esnault P, Nee L, Signouret T, Jaussaud N, Kerbaul F. Reverse Takotsubo cardiomyopathy after iatrogenic epinephrine injection requiring percutaneous extracorporeal membrane oxygenation. *Can J Anaesth* 2014;**61**:1093–1097.
35. Flam B, Broome M, Frenckner B, Branstrom R, Bell M. Pheochromocytoma-induced inverted Takotsubo-like cardiomyopathy leading to cardiogenic shock successfully treated with extracorporeal membrane oxygenation. *J Intensive Care Med* 2015;**30**: 365–372.
36. Beneduce A, Fausta Bertoldi L, Melillo F, Baldetti L, Spoladore R, Slavich M, Oppizzi M, Margonato A, Pappalardo F. Mechanical circulatory support with impella percutaneous ventricular assist device as a bridge to recovery in Takotsubo syndrome complicated by cardiogenic shock and left ventricular outflow tract obstruction. *JACC Cardiovasc Interv* 2019;**12**:e31–e32.
37. Napp LC, Westenfeld R, Möller JE, Pappalardo F, Ibrahim K, Bonello L, Wilkins C, Pershad A, Mannino SF, Schreiber TL, Hall PA, Medjania AM, Haurand JM, Sieweke JT, Schäfer A, Grines CL, Burkhoff D, Moses JW, Ohman EM, O'Neill VVW, Kapur NK, Bauersachs J. Impella mechanical circulatory support for Takotsubo syndrome with shock: a retrospective multicenter analysis. *Cardiovasc Revasc Med* 2022;**40**: 113–119.
38. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, de Waha A, Richardt G, Hennersdorf M, Empen K, Fuernau G, Desch S, Eitel I, Hambrecht R, Lauer B, Böhm M, Ebel H, Schneider S, Werdan K, Schuler G; Intraaortic Balloon Pump in cardiogenic shock II (IABP-SHOCK II) trial investigators. Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of a randomised, open-label trial. *Lancet* 2013;**382**:1638–1645.
39. Miller PE, Bromfield SG, Ma Q, Crawford G, Whitney J, DeVries A, Desai NR. Clinical outcomes and cost associated with an intravascular microaxial left ventricular assist device vs intra-aortic balloon pump in patients presenting with acute myocardial infarction complicated by cardiogenic shock. *JAMA Intern Med* 2022;**182**:926–933.
40. Singh K, Carson K, Shah R, Sawhney G, Singh B, Parsaik A, Gilutz H, Usmani Z, Horowitz J. Meta-analysis of clinical correlates of acute mortality in Takotsubo cardiomyopathy. *Am J Cardiol* 2014;**113**:1420–1428.
41. Santoro F, Carapelle E, Cieza Ortiz SI, Musaico F, Ferraretti A, d'Orsi G, Specchio LM, Di Biase M, Brunetti ND. Potential links between neurological disease and Tako-tsubo cardiomyopathy: a literature review. *Int J Cardiol* 2013;**168**:688–691.
42. Randhawa VK, Al-Fares A, Tong MZY, Soltész EG, Hernandez-Montfort J, Taimeh Z, Weiss AJ, Menon V, Campbell J, Cremer P, Estep JD. A pragmatic approach to weaning temporary mechanical circulatory support: a state-of-the-art review. *JACC Heart Fail* 2021;**9**:664–673.