SUPPLEMENTARY DATA

Table 1 of the supplementary data. Diagnostic criteria for tako-tsubo syndrome (TTS) according to Mayo Clinic Criteria, Heart Failure Association of the European Society of Cardiology, and InterTAK Diagnostic Criteria

Revised Mayo Clinic Criteria (Reference 1)
1. Transient hypokinesis, akinesis, or dyskinesis of the left ventricular (LV) mid segments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always, present. (a)
2. Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture. (b)
3. New electrocardiographic abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin.
4. Absence of pheochromocytoma or myocarditis.
Heart Failure Association–European Society of Cardiology Criteria (Reference 3)
1. Transient regional wall motion abnormalities of the LV or right ventricle myocardium, which are frequently, but not always, preceded by a stressful trigger (emotional or physical).
2. The regional wall motion abnormalities usually (c) extends beyond a single epicardial vascular distribution, and often result in circumferential dysfunction of the ventricular segments involved.
3. The absence of culprit atherosclerotic coronary artery disease, including acute plaque rupture, thrombus formation, coronary dissection, or other pathological conditions to explain the pattern of temporary LV dysfunction observed (eg, hypertrophic cardiomyopathy, viral myocarditis).
4. New and reversible electrocardiography abnormalities (ST-segment elevation, ST-segment depression, left bundle branch block (LBBB), (d) T-wave inversion, and/or QTc prolongation) during the acute phase (3 months).

5. Significantly elevated serum natriuretic peptide (B-type natriuretic peptide [BNP] or N-terminal pro B-type natriuretic peptide [NT-proBNP]) during the acute phase.

6. Positive but relatively small elevation in cardiac troponin measured with a conventional assay (ie, disparity between the troponin level and the amount of dysfunctional myocardium present). (e)

7. Recovery of ventricular systolic function on cardiac imaging at follow-up (3 to 6 months). (f)

International Tako-tsubo Diagnostic Criteria (InterTAK Diagnostic Criteria) (Reference 5)

1. Patients show transient LV dysfunction (hypokinesia, akinesia, or dyskinesia) presenting as apical ballooning or midventricular, basal, or focal wall motion abnormalities. Right ventricular involvement can be present. Besides these regional wall motion patterns, transitions between all types can exist. The regional wall motion abnormality usually extends beyond a single epicardial vascular distribution; however, rare cases can exist where the regional wall motion abnormality is present in the subtended myocardial territory of a single coronary artery (focal TTS). (g)

2. An emotional, physical, or combined trigger can precede the TTS event, but this is not obligatory.

3. Neurologic disorders (eg, subarachnoid hemorrhage, stroke/transient ischemic attack, or seizures) as well as pheochromocytoma may serve as triggers for TTS.

4. New electrocardiogram (ECG) changes are present (ST-segment elevation, ST-segment depression, T-wave inversion, and QTc prolongation); however, rare cases exist without any ECG changes.

5. Levels of cardiac biomarkers (troponin and creatine kinase) are moderately elevated in most cases; significant elevation of brain natriuretic peptide is common.

6. Significant coronary artery disease is not a contraindication in TTS.

7. Patients have no evidence of infectious myocarditis. (h)

8. Postmenopausal women are predominantly affected.

a) There are rare exceptions to these criteria, such as those patients in whom the regional wall motion abnormality is limited to a single coronary territory. *b)* It is possible that a patient with obstructive coronary atherosclerosis may also develop TTS. However, this is very rare in our experience and in the

published literature, perhaps because such cases are misdiagnosed as ACS. *c)* Acute, reversible dysfunction of a single coronary territory has been reported. *d)* LBBB may be permanent after TTS but should also alert clinicians to exclude other cardiomyopathies. T-wave changes and QTc prolongation may take many weeks to months to normalize after recovery of LV function. *e)* Troponin-negative cases have been reported but are atypical. *f)* Small apical infarcts have been reported. Bystander subendocardial infarcts have been reported, involving a small proportion of the acutely dysfunctional myocardium. These infarcts are insufficient to explain the acute regional wall motion abnormality observed. *g)* Wall motion abnormalities may remain for a prolonged period, or documentation of recovery may not be possible; for example, death before evidence of recovery is captured. *h)* Cardiac magnetic resonance imaging is recommended to exclude infectious myocarditis and confirm the diagnosis of TTS.

ACS, acute coronary syndrome; BNP, B-type natriuretic peptide; LBBB, left bundle branch block; LV, left ventricle; NT-proBNP, N-terminal pro–B-type natriuretic peptide; TTS, tako-tsubo syndrome.

Table 2 of the supplementary data. Randomized clinical trials on TTS

1. Efficacy and safety of levosimendan in Chinese elderly patients with Tako-tsubo syndrome. Not registered. Randomized and double-blinded design. 200 consecutive patients (> 65 years) with TTS randomly assigned into a levosimendan group (n = 100) vs control group (n = 100). Left ventricular ejection fraction was significantly higher, and New York Heart Association (NYHA) class and BNP levels were significantly lower in the levosimendan group at 30 and 180 days than those in the control group. Concern: all patients (100%) were in NYHA functional class IV at diagnosis, yet mortality at 180 days was only 1% and 8%, respectively.[1]

2. The BROKEN-SWEDE-HEART (Optimized Pharmacological Treatment for Broken Heart [Tako-tsubo] syndrome). ClinicalTrials.gov ID: NCT04666454. PI: Elmir Omerovic MD. Sweden. Phase 2 trial with factorial 2x2 design. Sample size 1,000 patients. Randomization 1: Adenosine and Dipyridamole. Primary endpoint wall motion score index (WMSI) at 48-96h (sample size 200 patients). Randomization 2: Apixaban. Primary endpoint the occurrence of any thromboembolic event (1000 patients).[2]

3. The N-AcetylCysteine and RAMipril in Tako-tsubo Syndrome Trial (NACRAM). DOI: 10.1016/j.cct.2019.105894. PI: John Horowitz MD. Australia. NACRAM is a multicenter, randomized, placebo-controlled trial, sequentially testing early use of intravenous N-acetylcysteine and subsequently oral ramipril for 12 weeks. Sample size of 80 patients. The rationale for utilizing these agents is related to their effects on limiting nitrosative stress and expression of the inflammasome activator thioredoxin interacting protein (TXNIP). **End points: 1)** resolution of myocardial edema (by cardiac MRI at 24 hours) and 2) improvement in left ventricular systolic function (global longitudinal strain on echocardiography at 3 months).[3]

4. Adenosine to Rapidly Reverse Left Ventricle Impairment in Tako-tsubo Syndrome (TITAN). ClinicalTrials.gov ID: NCT02867878. PI: Matteo Tebaldi MD. Italy. Systemic infusion of

adenosine at 140 µg/kg/min for 3 minutes vs saline with 48-hour echocardiographic assessment of left ventricular ejection fraction (LVEF) (primary endpoint) and wall motion score index (WMSI). This study was interrupted after 2 years because only 5 patients (target 40) could be included.

5. Sympathetic and Vascular Function in Tako-tsubo Syndrome (SAFT). ClinicalTrials.gov ID: NCT05768542. PI: Jonas 9 MD, Karolinska Institute. The primary objective of this prospective "observational" study is to compare muscle sympathetic nerve activity at rest and during stress between female patients with TTS and healthy matched volunteers. Participants will be examined with muscle sympathetic nerve activity recording in the peroneal nerve at rest and during the cold pressor test. After intravenous injection of metoprolol or placebo (saline) in a 1:1 randomized fashion, muscle sympathetic nerve recording at rest and during stress will be repeated. Active comparator: TTS. Control: Patients with TTS receiving beta-blockers. Assessment of muscle sympathetic nerve activity at rest and during the cold pressor test.

6. Life-Style Interventions for Modulating the Brain Phenotype of Tako-tsubo Cardiomyopathy - the BREAKOUT Study. ClinicalTrials.gov ID: NCT05530135. University of Aberdeen. TTS patients and controls. Randomized trial with factorial assignment. Open label. Three-arm pilot feasibility study. Active Comparator: Exercise Group. TTS patients who will undergo an exercise program in addition to standard care. Outcome measure: hippocampal volume change as determined by brain MRI at ≤ 3 weeks of TTS diagnosis and repeated at completion of the 12-week intervention.

7. Physical Exercise and Mental Wellbeing Rehabilitation for Acute Stress-Induced Tako-tsubo Cardiomyopathy: The PLEASE Study. ClinicalTrials.gov ID: NCT04425785. University of Aberdeen. Randomized controlled study. TTS patients will be randomized into one of the following groups: Exercise Arm, Cognitive Behavioral Arm, Standard Clinical Care. Experimental: Physical Exercise Group. A structured exercise program for 12 weeks.

Experimental: Cognitive behavioral therapy for 12 weeks. No Intervention: Standard clinical care.

8. The e-mental health treatment in Stockholm myocardial infarction with nonobstructive coronaries or Tako-tsubo syndrome study (E-SMINC): a study protocol for a randomized controlled trial. ClinicalTrials.gov ID: NCT04178434. PI: Erik M G Olsson MD. Randomized controlled trial, where 90 patients with a discharge diagnosis of either myocardial infarction with nonobstructive coronary arteries (MINOCA) or TTS, who also report symptoms of stress or anxiety, will be randomized 2-6 weeks after their cardiac event. The treatment consists of 10 weeks of Internet-based cognitive behavioral therapy and starts immediately after randomization for the treatment group. The control group receives usual care. Main outcomes are symptoms of anxiety assessed by different scales.

These are recently designed randomized studies on TTS. Some of them have already been canceled due to enrollment difficulties. Others are currently starting the inclusion phase. Some studies have been listed in repositories (clinical.trials.gov) or have published only the "design" paper.[2,3] The only published study[1] has a major potential flaw (excellent survival with all patients initially in cardiogenic shock) and it is usually not included in the academic reviews on the topic.

REFERENCES OF THE SUPPLEMENTARY DATA

1. Guo Y, Zhou C, Yang X. Efficacy and safety of levosimendan in Chinese elderly patients with Takotsubo syndrome. *Ann Transl Med*. 2018;6:438.

2. Omerovic E, James S, Erlinge D, et al. Rationale and design of BROKEN-SWEDEHEART: a registry-based, randomized, parallel, open-label multicenter trial to test pharmacological treatments for broken heart (takotsubo) syndrome. *Am Heart J.* 2023;257:33-40.

3. Ong GJ, Nguyen TH, Stansborough J, et al. The N-AcetylCysteine and RAMipril in Takotsubo Syndrome Trial (NACRAM): Rationale and design of a randomised controlled trial of sequential N-Acetylcysteine and ramipril for the management of Takotsubo Syndrome. *J Contemp Clin Trials.* 2020;90:105894.