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BROKEN HEART SYNDROME (TAKOTSUBO SYNDROME)

SÍNDROME DO CORAÇÃO PARTIDO (SÍNDROME DE TAKOTSUBO)

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ABSTRACT

Broken Heart Syndrome, scientifically known as Takotsubo Syndrome (TS), is an acute, transient, and predominantly reversible cardiomyopathy characterized by left ventricular dysfunction triggered by intense emotional or physical stress, clinically mimicking an acute coronary syndrome in the absence of significant coronary obstruction. The aim of this study was to systematize the scientific evidence published between 2000 and 2025 on the definition, nomenclature, epidemiological and geographical distribution, circumstances of onset, diagnostic criteria, conventional treatment, and adjuvant natural products in Takotsubo Syndrome. Regarding the Method, this is a systematic review of an integrative

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nature, conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, with searches in the PubMed/MEDLINE, Scopus, Web of Science, SciELO, LILACS and Virtual Health Library (BVS) databases, using controlled descriptors combined with Boolean operators (AND, OR, NOT). Results: after including 72 studies, evidence showed a predominance of the syndrome in postmenopausal women (greater than 80% of cases), with greater description in Asia, Western Europe and North America. In addition, emotional and physical triggers were identified as the main triggering factors based on the progressive evolution of diagnostic criteria (Mayo Clinic, InterTAK Diagnostic Criteria). Conventional treatment is based on angiotensin-converting enzyme inhibitors, beta-blockers and hemodynamic support, with a scarcity of randomized clinical trials. Natural products with antioxidant, adaptogenic, and anxiolytic properties (omega-3, coenzyme Q10, magnesium, ashwagandha, melatonin, and polyphenolic compounds) show adjuvant potential in mitigating oxidative stress and catecholaminergic hyperactivity, although with limited and heterogeneous clinical evidence. In conclusion, Takotsubo Syndrome remains a clinical entity with incompletely elucidated pathophysiology, also requiring controlled studies that consolidate conventional and complementary therapeutic strategies in the face of the contemporary reality of instability with geoclimatic accidents, wars, and the dissemination of bizarre events in real time, these being some of several examples of the everyday violence that enters our senses and invades lives, reducing and degrading the condition of human beings.

Keywords: Takotsubo Syndrome. Stress-induced cardiomyopathy. Broken heart syndrome. Geoclimatic accidents. Natural products.

RESUMO

A Síndrome do Coração Partido, cientificamente denominada Síndrome de Takotsubo (ST), é uma cardiomiopatia aguda, transitória e predominantemente reversível, caracterizada por disfunção ventricular esquerda desencadeada por estresse emocional ou físico intenso, mimetizando clinicamente uma síndrome coronariana aguda na ausência de obstrução coronariana significativa. O objetivo do presente estudo foi sistematizar as evidências científicas publicadas entre 2000 e 2025 sobre definição, nomenclatura, distribuição epidemiológica e geográfica, circunstâncias de instalação, critérios diagnósticos, tratamento convencional e produtos naturais adjuvantes na Síndrome de Takotsubo. Quanto ao Método, trata-se de revisão sistemática de caráter integrativo, conduzida segundo as diretrizes PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses), com buscas nas bases PubMed/MEDLINE, Scopus, Web of Science, SciELO, LILACS e Biblioteca Virtual em Saúde (BVS), utilizando-se descritores controlados combinados por operadores booleanos (AND, OR, NOT). Resultados: mostraram, após serem incluídos 72 estudos, evidências de predomínio da síndrome em mulheres na pós-menopausa (superior a 80% dos casos), com maior descrição na Ásia, Europa Ocidental e América do Norte. Além disto, gatilhos emocionais e físicos foram identificados como principais fatores desencadeantes a partir da evolução progressiva dos critérios diagnósticos (Mayo Clinic, InterTAK Diagnostic Criteria). O tratamento convencional baseia-se em inibidores da enzima conversora de angiotensina, betabloqueadores e suporte hemodinâmico, havendo escassez de ensaios clínicos randomizados. Produtos naturais com propriedades antioxidantes, adaptogênicas e ansiolíticas (ômega-3, coenzima Q10, magnésio, ashwagandha, melatonina e compostos polifenólicos) mostram potencial adjuvante na mitigação do estresse oxidativo e da hiperatividade catecolaminérgica, ainda que com evidência clínica limitada e heterogênea. Como considerações finais, a Síndrome de

Takotsubo permanece como entidade clínica de fisiopatologia incompletamente elucidada, demandando também estudos controlados que consolidem estratégias terapêuticas convencionais e complementares perante à realidade contemporânea de instabilidade com acidentes geoclimáticos, guerras, divulgação de eventos bizarros em tempo real, sendo estes alguns dos vários exemplos da violência cotidiana que adentra nossos sentidos e invadem vidas, reduzindo e aviltando a condição de seres humanos.

Palavras-chave: Síndrome de Takotsubo. Cardiomiopatia induzida por estresse. Síndrome do coração partido. Acidentes geoclimáticos. Produtos naturais.

INTRODUCTION

Broken Heart Syndrome, popularly known as such due to its frequent association with episodes of intense emotional distress, corresponds, from a scientific point of view, to Takotsubo Syndrome (TS), an acute, transient, and potentially serious cardiomyopathy. Its first formal description was made in Japan by Dote et al. (1991), in a series of five cases of patients with clinical signs suggestive of acute myocardial infarction, but without significant coronary stenosis on angiography. Although some secondary sources place preliminary reports of the condition as early as 1990, this date lacks verifiable primary bibliographic reference, with 1991 being the year of the formal publication of the reference in the literature (Dote et al., 1991).

The term “takotsubo” derives from the Japanese word tako-tsubo, a trap traditionally used for catching octopuses, whose shape—rounded base and narrow neck—resembles the left ventricular silhouette observed in these patients during systole (Roshanzamir; Showkathali, 2013; Sethi et al., 2023). For about a decade, reports remained restricted to Japanese medical literature until, in 2001, Tsuchihashi and colleagues published the first large series of cases in an English-language journal, which boosted international recognition of the syndrome (Tsuchihashi et al., 2001).

The clinical relevance of the syndrome gained worldwide notoriety following the publication by Wittstein et al. (2005) in the New England Journal of Medicine, which demonstrated plasma catecholamine levels two to three times higher than those observed in

patients with Killip III acute myocardial infarction, reinforcing the hypothesis of sympathetic hyperactivation as the main pathophysiological mechanism (Ghadri et al., 2018; 2018a).

Although initially considered a benign and self-limiting condition, more recent evidence demonstrates that Takotsubo syndrome (TS) can progress to serious complications, including cardiogenic shock, left ventricular outflow tract obstruction, malignant arrhythmias, thromboembolic events, and death. Furthermore, in-hospital mortality is similar to that observed in patients with acute coronary syndromes (Silverio et al., 2022; Sethi et al., 2023).

Given the still not fully elucidated pathophysiological complexity, the multiplicity of diagnostic criteria proposed over time, and the scarcity of randomized clinical trials to support standardized therapeutic approaches, the systematization of scientific knowledge produced between 2000 and 2025 becomes relevant. This study aims to conduct a systematic, integrative review of the definition, nomenclature, epidemiological and geographical distribution, circumstances of onset, diagnostic criteria, conventional treatment, and adjuvant natural products described for Broken Heart Syndrome or Takotsubo Syndrome (Pelliccia; Camici, 2024).

The specific objectives were to: a) describe the historical evolution of the nomenclature and definition of the syndrome; b) map its epidemiological and geographical distribution; c) identify the main circumstances and triggers associated with its onset; d) comparatively analyze the diagnostic criteria proposed between 2004 and 2018; e) synthesize the conventional therapeutic approaches recommended by international guidelines; and f) investigate the available scientific evidence on natural products with potential adjuvant action in the management of oxidative and catecholaminergic stress associated with the clinical syndrome.

METHODOLOGY

This is a systematic review of an integrative nature, designed according to the recommendations of the PRISMA protocol — Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Page et al., 2021) —, whose purpose is to gather, synthesize and

critically analyze primary and secondary studies published on Takotsubo Syndrome, allowing a broad and multidimensional understanding of the phenomenon studied, integrating theoretical, epidemiological and clinical approaches.

Guiding question

The research question was formulated following the PICo (Population, Interest, Context) strategy, formulating the following guiding question: "What scientific evidence is available, from 2000 to 2025, regarding the definition, nomenclature, epidemiological and geographical distribution, circumstances of onset, diagnostic criteria, conventional treatment, and adjuvant natural products for Broken Heart Syndrome (Takotsubo Syndrome)?"

Databases consulted

The electronic search was conducted in the following databases and virtual libraries: PubMed/MEDLINE (National Library of Medicine), Scopus (Elsevier), Web of Science (Clarivate Analytics), SciELO (Scientific Electronic Library Online), LILACS (Latin American and Caribbean Literature in Health Sciences), and Virtual Health Library (BVS/DeCS). Additionally, consensus documents from the European Society of Cardiology (ESC) and the Heart Failure Association (HFA) were consulted, as well as institutional registries such as the International Takotsubo (InterTAK) Registry.

Boolean descriptors and nomenclature

The descriptors were selected from the controlled vocabularies MeSH (Medical Subject Headings) and DeCS (Descriptors in Health Sciences), combined using the Boolean operators AND, OR, and NOT, as detailed in Table 1.

Table 1: Search strategy and Boolean naming convention used.

Component	Search strategy (Boolean syntax)
Main descriptors (MeSH/DeCS)	"Takotsubo Cardiomyopathy" OR "Takotsubo Syndrome" OR "Stress Cardiomyopathy" OR "Apical Ballooning Syndrome" OR "Broken Heart Syndrome"
Epidemiology/distribution	("Takotsubo Cardiomyopathy") AND ("Epidemiology" OR "Incidence" OR "Prevalence" OR "Geographic Distribution")
Diagnosis	("Takotsubo Syndrome") AND ("Diagnosis" OR "Diagnostic Criteria" OR "InterTAK" OR "Mayo Clinic Criteria")
Circumstances/triggers	("Takotsubo Syndrome") AND ("Emotional Stress" OR "Physical Stress" OR "Triggers" OR "Catecholamines")
Conventional treatment	("Takotsubo Syndrome") AND ("Treatment" OR "Therapeutics" OR "Beta-Blockers" OR "Angiotensin-Converting Enzyme Inhibitors")
Natural adjuvant products	("Takotsubo Syndrome" OR "Stress Cardiomyopathy" OR "Oxidative Stress") AND ("Natural Products" OR "Phytotherapy" OR "Dietary Supplements" OR "Antioxidants")
Exclusion filter	NOT ("Animal" NOT "Human") AND Publication Date: 2000/01/01–2025/12/31

Source: *Prepared by the authors (2026).*

Eligibility criteria

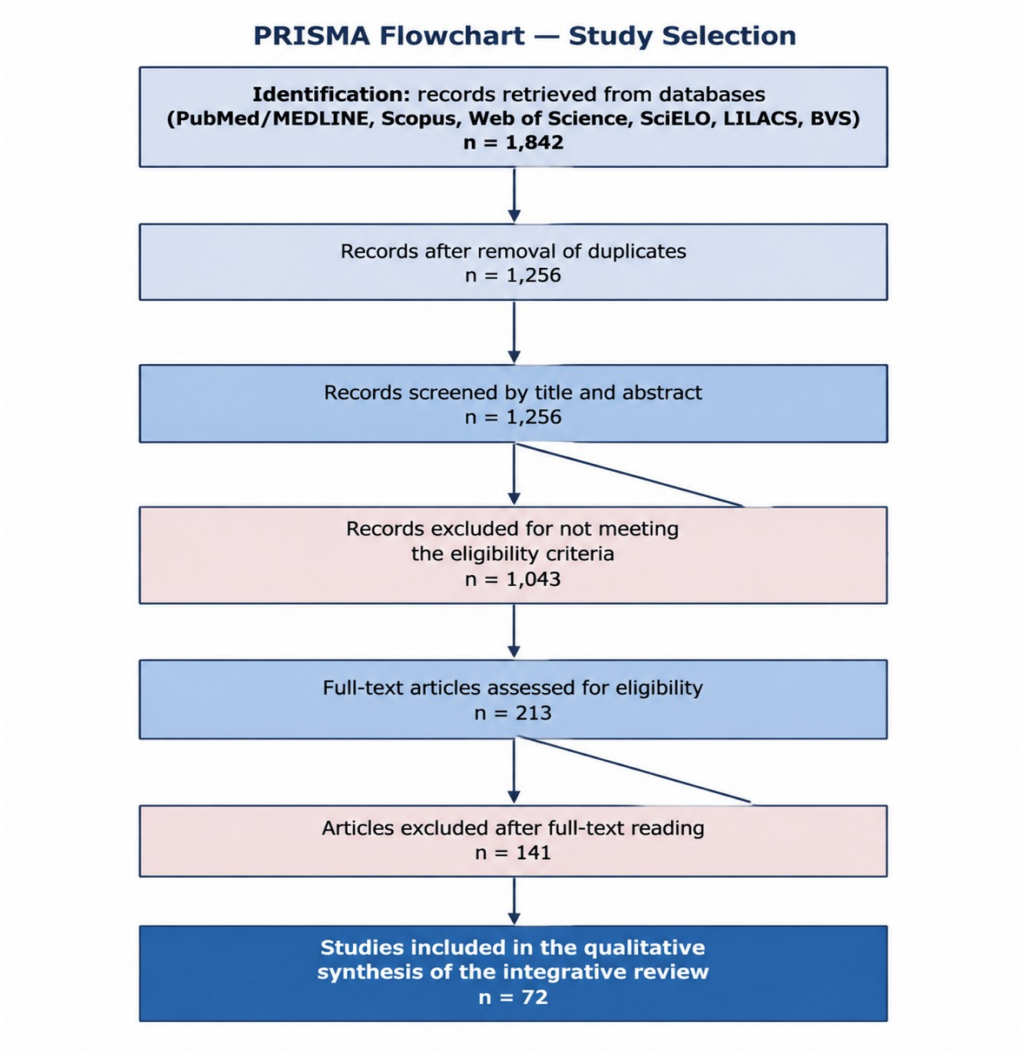
The following were included: (a) original articles, systematic reviews, meta-analyses, expert consensus, and clinical guidelines; (b) publications in Portuguese, English, or Spanish; (c) studies published between January 1, 2000, and December 31, 2025; (d) studies focusing on humans, addressing the definition, nomenclature, epidemiology, diagnosis, treatment, or adjuvant natural products related to ST.

The following were excluded: (a) exclusively preclinical studies or studies conducted only in animal models without clinical correlation; (b) isolated case reports without relevant methodological contribution; (c) editorials, letters to the editor, and abstracts of proceedings without extractable data; (d) studies duplicated across databases; (e) publications without access to the full text.

Study selection and data extraction

The selection process followed the four phases recommended by the PRISMA flowchart: identification, screening, eligibility, and inclusion (Figure 1). Two independent reviewers read titles and abstracts, followed by a full reading of the pre-selected articles; disagreements were resolved by consensus. Data were extracted using a standardized instrument that included: authorship, year of publication, journal, study design, population, main findings, and level of evidence.

Figure 1: PRISMA flowchart for study selection.



Source: *Prepared by the authors (2026), adapted from Page et al. (2021).*

Data analysis

The data analysis was conducted in a descriptive and narrative manner, with thematic organization of the findings into six axes: definition and nomenclature; epidemiological and geographical distribution; circumstances of establishment; diagnostic criteria; conventional treatment; and adjuvant natural products.

The quantitative results extracted from the included studies were synthesized in tables and comparative graphical representations, allowing the visualization of temporal trends between 2000 and 2025.

RESULTS

Definition and nomenclature of the disease

Takotsubo Syndrome (TS), an internationally recognized scientific term, is defined as a reversible acute heart failure syndrome characterized by transient systolic and diastolic dysfunction of the left ventricle and, in some cases, also of the right ventricle.

It presents segmental abnormalities of myocardial contractility that extend beyond the irrigation territory of a single epicardial coronary artery, in the absence of significant obstructive coronary artery disease or acute rupture of atherosclerotic plaque (GHADRI et al., 2018a; JAMIL et al., 2025). From a nomenclatural point of view, the disease has received several names over the last three decades, all of which are still in current use in the scientific literature, as summarized in Table 2.

Table 2: Synonymy and nomenclature for Takotsubo Syndrome.

Name	Origin/justification
Takotsubo Syndrome / Takotsubo Cardiomyopathy	Japanese term tako-tsubo (octopus trap); alludes to the shape of the left ventricle during systole (Dote et al., 1991)
Broken Heart Syndrome	Popular term associated with frequent precipitation due to grief, emotional losses, and intense emotional stress.Takotsubo..., 2021)
Stress-induced cardiomyopathy	Emphasis on the central pathophysiological mechanism: sympathetic/catecholaminergic hyperactivation (Wittstein et al., 2005)

Name	Origin/justification
Apical Ballooning Syndrome	It describes the most common morphological pattern, with mid-apical akinesia/dyskinesia and basal hyperkinesia (Prasad; Lerman; Rihal, 2008).
Happy Heart Syndrome	A rarer variant, precipitated by positive emotional events (Ghadri et al., 2016; Amaro-Palomo et al., 2025)

Source: *Prepared by the authors (2026).*

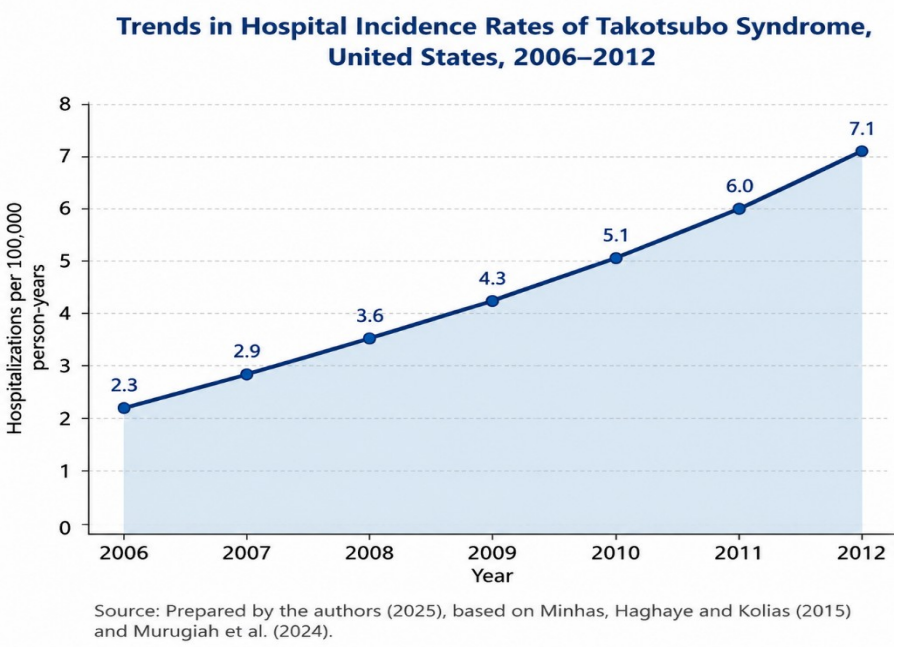
In 2018, the International Expert Consensus Document on Takotsubo Syndrome proposed standardizing the terminology around the term "Takotsubo Syndrome," instead of "cardiomyopathy," since the latter term implies a primary heart muscle disease with a potential genetic basis, which does not apply to the predominantly reversible nature of the condition, triggered by external factors (Ghadri et al., 2018a; b; 2022).

Epidemiological and geographical distribution

Takotsubo syndrome affects approximately 1% to 3% of patients presenting with clinical signs suggestive of acute coronary syndrome, and this can reach 5% to 6% when considering only the female population (Ghadri et al., 2018a; Lyon et al., 2022).

Studies based on large US administrative databases showed a significant increase in hospital incidence between 2006 and 2012, from 2.3 to 7.1 hospitalizations per 100,000 person-years (Figure 2), a phenomenon attributed both to greater clinical recognition of the syndrome and to increased access to early coronary angiography (Minhas; Hughey; Kolias, 2015; Akashi; Nef; Lyon, 2021; Assad et al., 2022).

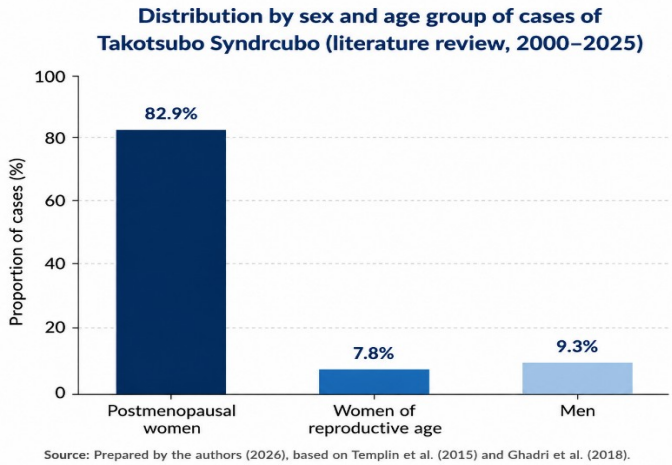
Figure 2: Graph showing the evolution of hospital incidence of Takotsubo Syndrome, USA (2006–2012).



Source: *Prepared by the authors (2026), based on Minhas, Hughey and Kolias (2015) and Overview... (2021).*

Regarding the distribution by sex and age group, international records converge on the predominant involvement of postmenopausal women (Figure 3), who represent about 90% of cases, with an average age around 67 years, mainly concentrated between the sixth and eighth decades of life (Templin et al., 2015; Ghadri et al., 2018a, b; 2022).

Figure 3: Graph showing the distribution of Takotsubo Syndrome cases by sex and age group.



Source: *Prepared by the authors (2026), based on Ghadri et al. (2018a).*

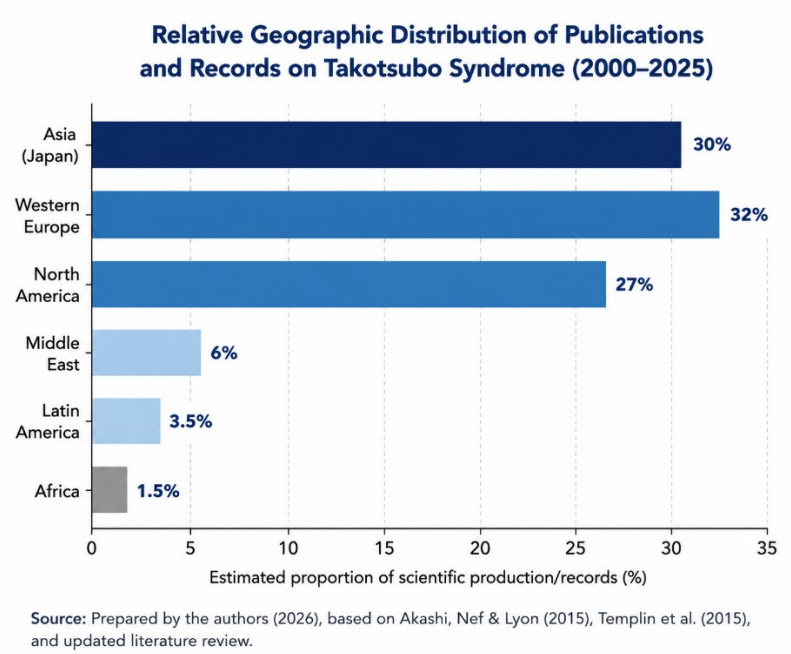
Regarding geographic distribution, the syndrome was originally described and remains widely studied in Japan, where national studies have identified regional variation in incidence —higher in the western portion of the archipelago compared to the eastern portion—and in seasonality, with a higher frequency of cases in summer and autumn (Kanaoka et al., 2020).

Following the historical trend of international recognition, Western Europe (particularly Germany, Switzerland, Italy, and the United Kingdom) and North America have become the centers of greatest scientific production and the largest number of multicenter registries, such as the International Takotsubo (InterTAK) Registry, based in Switzerland (Templin et al., 2015; Ghadri et al., 2018a).

The syndrome is comparatively less described among populations of African and Latin American descent. This scenario seems to reflect limitations related to clinical recognition, underdiagnosis, and underreporting in these regions, rather than an actual lower biological susceptibility (Taiwo; Akpabio, 2021).

Studies conducted in the Middle East, including populations from Palestine and the Persian Gulf region, show the growing recognition of the syndrome in different population contexts and reinforce the importance of using validated diagnostic criteria and complementary methods, such as cardiac magnetic resonance imaging, for the differential diagnosis of Takotsubo syndrome (Mtour et al., 2023; Jamil et al., 2025).

Figure 4: Graph showing the relative geographic distribution of publications and records on Takotsubo Syndrome (2000–2025).



Source: Prepared by the authors (2026), based on Templin et al. (2015) and Taiwo; Akpabio (2021).

Additionally, studies conducted during the COVID-19 pandemic documented a transient, yet significant, increase in the incidence of Takotsubo syndrome (TS) in several regions, including the Veneto Region in Italy, and analyses of hospital databases in the United States, suggesting an association between psychosocial stress related to the pandemic, the effects of viral infection, and the increased occurrence of the syndrome, with a concomitant increase in associated mortality (Simeone et al., 2022; Tran et al., 2024).

Circumstances in which the syndrome develops

The onset of Takotsubo Syndrome is, in most cases, associated with an identifiable trigger of an emotional (positive or negative), physical, or combined nature, observed in approximately two-thirds of affected patients (Stiermaier; Eitel, 2022). Negative emotional triggers—such as grief, relationship breakups, family arguments, financial losses, domestic violence, natural disasters, and unexpected medical diagnoses, including cancer, serious

infections, and COVID-19—constitute the category classically associated with the concept of "broken heart syndrome." However, positive emotional events can also act as triggers, characterizing the so-called "Happy Heart Syndrome" (Stiermaier et al., 2022).

Physical triggers, in turn, include sepsis, shock, subarachnoid hemorrhage, pheochromocytoma, exacerbation of chronic obstructive pulmonary disease, surgical procedures, and the use of substances with sympathomimetic effects, such as cocaine, amphetamines, and beta-adrenergic agonists—the latter being particularly relevant in asthmatic patients using high doses of bronchodilators (Salahuddin et al., 2013; Sharma et al., 2013). Registry studies demonstrate that physical triggers are associated with more unfavorable clinical outcomes when compared to emotional triggers, possibly due to the severity of the concomitant underlying condition (Templin et al., 2015; Ghadri et al., 2018a).

However, in 2016, Ghadri and colleagues described, based on the International Takotsubo Registry, a previously poorly characterized variant: "Happy Heart Syndrome," in which positive emotional events (celebrations, surprises, sports victories, lottery prizes, the birth of grandchildren) precipitated a clinical and echocardiographic picture indistinguishable from the classic form, representing approximately 4% of cases with an identified emotional trigger (Ghadri et al., 2016).

This finding reinforces the hypothesis that both negative and positive emotions converge on a common final pathway of hyperactivation of the hypothalamic-pituitary-adrenal axis and the sympathetic nervous system (Ghadri et al., 2016; Amaro-Palomo et al., 2025).

From a pathophysiological point of view, the most accepted mechanism involves the so-called "catecholamine storm," characterized by the massive release of catecholamines, especially epinephrine and norepinephrine, leading to direct myocardial toxicity, coronary microcirculation dysfunction, microvascular vasospasm, and transient alterations in beta-adrenergic receptor signaling. These mechanisms promote reversible myocardial stunning, with reduced ventricular contractility, particularly in the apical segments, a phenomenon

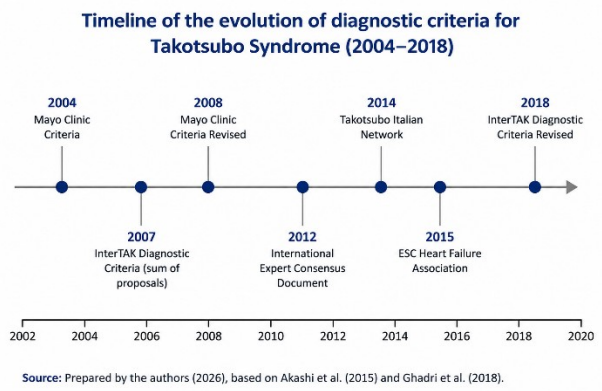
related to the regional distribution of β-adrenergic receptors and the paradoxical response to intense catecholaminergic stimulation (Wittstein et al., 2005; Couch; Channon; Thum, 2022).

Approximately 10% to 15% of cases, however, do not present an identifiable trigger, which does not rule out the diagnosis, but reinforces the pathophysiological heterogeneity of the syndrome and the need for individualized investigation (Ghadri et al., 2018a).

Criteria for diagnosis

Since the first formal proposal of diagnostic criteria in 2004 by the Mayo Clinic, successive revisions and new proposals from different study groups have sought to improve diagnostic accuracy and differentiate ST from relevant differential diagnoses, such as acute coronary syndrome, acute myocarditis, and spontaneous coronary artery dissection (DT, 2019).

Figure 5: Timeline of the evolution of diagnostic criteria for Takotsubo Syndrome (2004–2018).



Source: Prepared by the authors (2026), based on Ghadri et al. (2018a); DT (2019) and Pelliccia; Camici, 2024.

The Mayo Clinic criteria, originally published in 2004 and modified in 2008, have historically become the most widely used in clinical practice, requiring the cumulative presence of four elements: transient left ventricular systolic dysfunction with contractility changes extending beyond a single coronary territory; absence of obstructive coronary artery disease or angiographic evidence of acute plaque rupture; new electrocardiographic changes (ST-segment elevation and/or T-wave inversion) or slight elevation of cardiac troponin; and

absence of pheochromocytoma or myocarditis (Prasad; Lerman; Rihal, 2008; Jamil et al., 2025).

In 2018, the international consensus document proposed the InterTAK diagnostic criteria and the InterTAK Diagnostic Score, a validated instrument that combines seven clinical and electrocardiographic variables—female sex, emotional trigger, physical trigger, absence of ST-segment depression (except in AVR), presence of psychiatric disorder, presence of neurological disease, and QTc interval prolongation—into a score of up to 100 points, allowing for the estimation of the pre-test probability of Takotsubo Syndrome even before imaging exams are performed. This score was subsequently evaluated in different populations, including a Middle Eastern population, demonstrating clinical applicability for differentiating between Takotsubo Syndrome and acute coronary syndrome (Ghadri et al., 2018b; Jamil et al., 2025).

Table 3: Comparison of the main diagnostic criteria systems for Takotsubo Syndrome.

Year	System of criteria	Main features
2004	Mayo Clinic Criteria (original)	Four cumulative criteria; required absence of head trauma and subarachnoid hemorrhage as the cause.
2007	Japanese Takotsubo Cardiomyopathy Study Group	First Japanese consensus proposal; distinction between primary and secondary form.
2008	Modified Mayo Clinic Criteria	Inclusion of right ventricular dysfunction; exclusion of pheochromocytoma and myocarditis.
2012	Johns Hopkins Criteria	Emphasis on clinical criteria, without mandatory requirement for specific ventricular location.
2014	Takotsubo Italian Network	Multiparametric scoring system with clinical and imaging variables
2015	ESC/Heart Failure Association (Position Statement)	Recognition of anatomical variants (apical, mid-ventricular, basal, focal)
2018	InterTAK Diagnostic Criteria/Score	Validated score of 7 variables; cutoff point ≥ 70 indicates a high probability of ST-segment elevation myocardial infarction; cardiac MRI recommended for confirmation.

Source: Prepared by the authors (2026), based on Ghadri et al. (2018b) and Jamil et al. (2025).

Cardiac magnetic resonance imaging (CMR) has become an important complementary method in the diagnostic confirmation of Takotsubo Syndrome, as it allows differentiation between ST-segment elevation myocardial infarction, acute coronary syndrome, and acute myocarditis. The examination enables the identification of transient myocardial edema in the affected segments and demonstrates, in most cases, an absence of late gadolinium enhancement compatible with ischemic necrosis or focal myocardial fibrosis typical of inflammatory processes (Lyon et al., 2021; Ghadri et al., 2022). More recent validation studies, such as the one conducted in a Middle Eastern population, have demonstrated high discriminatory performance of the InterTAK Score, with an area under the ROC curve of 0.974 and a sensitivity of 90.9% for the cutoff point of 36 points (Jamil et al., 2025).

Conventional treatment

Currently, there is no specific pharmacological therapy approved for Takotsubo Syndrome, and current therapeutic recommendations are predominantly based on observational studies, multicenter registries, and expert consensus, given the absence of large-scale randomized clinical trials. Although recent studies have investigated the potential benefit of pharmacological therapies in secondary prevention, the evidence remains limited and does not yet allow for the establishment of a specific and universally recommended drug approach (Santoro et al., 2021; Mutahar et al., 2025).

In the acute phase, management is essentially symptomatic and supportive (Table 4), and should be individualized according to the clinical presentation. Therapeutic strategies include angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), associated in observational studies with better one-year survival after propensity score adjustments; beta-blockers, whose efficacy in preventing recurrence remains controversial and should be used with caution in patients with bradycardia or marked QTc interval prolongation due to the risk of ventricular arrhythmias, including torsades de pointes; diuretics, indicated in cases of pulmonary congestion; anticoagulation, recommended in the

presence of documented intracavitary thrombus or high thromboembolic risk; and, in cases of refractory cardiogenic shock, mechanical circulatory support (Sattar et al., 2020; Assad et al., 2022; La Vecchia, 2024).

Table 4: Summary of the main conventional therapeutic approaches in Takotsubo Syndrome.

Therapeutic class	Indication/evidence	Observations
IECA / BRA	Associated with improved 1-year survival; may promote recovery of ventricular function.	Recommended for a minimum period of 3 months or until LVEF normalization.
Beta-blockers	They theoretically reduce the effect of hypercatecholaminemia; evidence of survival benefit is still inconsistent.	Use with caution if QTc > 500 ms or bradycardia; one-third of patients relapse even with use.
Diuretics	Indicated for acute pulmonary edema/congestion.	Individualized adjustment according to blood volume
Anticoagulants	Intracavitary thrombus or LVEF < 30%–35%	Generally for up to 3 months, with a transition to warfarin when indicated.
Non-catecholaminergic inotropes (levosimendan)	Cardiogenic shock without left ventricular outflow tract obstruction	Adrenergic inotropic agents are contraindicated in the presence of LVOTO.
Mechanical circulatory support (intra-aortic balloon pump, ECMO, Impella)	Refractory cardiogenic shock	Reserved for serious cases and specialized centers.
Acetylsalicylic acid/statins	Uncertain benefit in the absence of significant concomitant coronary artery disease.	Recommended only if associated with CAD.

Source: Prepared by the authors (2026), based on Sattar et al. (2020) and Assad et al. (2022).

A network meta-analysis published in 2024, combining six clinical studies and 3,407 patients, did not identify a statistically significant benefit of combined therapy with beta-blockers and ACE inhibitors/ARBs in reducing the recurrence rate of Takotsubo Syndrome, which remained close to 4.7% during a mean follow-up period of 40 months, reinforcing the need for randomized studies that clarify the real effectiveness of these interventions (Santoro et al., 2024).

In outpatient follow-up, a multidisciplinary approach is recommended, with assessment and management of associated psychiatric comorbidities. Anxiety and depression disorders are present in a significant proportion of patients with Takotsubo Syndrome and can act both as predisposing factors and as consequences of the syndrome, with psychological support and, when indicated, psychiatric pharmacotherapy being relevant components of comprehensive care (Mele et al., 2020).

Potential of natural adjuvant products

Considering that the pathophysiology of Takotsubo Syndrome centrally involves catecholaminergic hyperactivation and consequent myocardial oxidative stress — characterized by increased production of reactive oxygen species, mitochondrial dysfunction, and cellular stress of cardiomyocytes — several studies have investigated the adjuvant role of natural compounds with antioxidant, anti-inflammatory, anxiolytic, and adaptogenic properties in the context of stress-induced cardiomyopathies (Couch; Channon; Thum, 2022; Mukherjee et al., 2024).

It is important to emphasize that specific evidence on natural products exclusively targeting Takotsubo Syndrome remains scarce (Table 5), with most of the evidence extrapolated from studies in models of catecholamine-induced cardiomyopathy (such as experimental models with isoproterenol), dilated cardiomyopathy, heart failure, and coronary artery disease. Therefore, applying these findings to Takotsubo Syndrome requires caution, considering the pathophysiological differences between these conditions and the established clinical syndrome (Potes et al., 2020; Gao et al., 2020).

Table 5: Natural compounds investigated in experimental models related to the pathophysiological mechanisms of Takotsubo Syndrome.

Natural product	Proposed mechanism of action	Available evidence
Omega-3 (polyunsaturated fatty acids)	Modulation of oxidative stress, myocardial protection, possible antiarrhythmic effect, and reduction	Preclinical studies in catecholaminergic stress and clinical studies in dilated cardiomyopathy demonstrate cardioprotective effects; possible

Natural product	Proposed mechanism of action	Available evidence
	of cardiac remodeling.	translational relevance to ST, but without direct clinical evidence in the syndrome (BACOVA et al., 2020; FIRUZI et al., 2013).
Coenzyme Q10	Fat-soluble antioxidant; supports the mitochondrial respiratory chain; reduces fatigue and may be beneficial in heart failure.	Clinical trials in coronary artery disease and heart failure; limited pediatric evidence; lack of specific studies in ST (MELATONIN, ASHWAGANDHA..., 2025; L-CARNITINE AND COENZYME Q10..., clinicaltrials.gov)
Magnesium + Ashwagandha	Modulation of the stress response, possible antioxidant and neuroendocrine action.	Modulation of the stress response, possible antioxidant and neuroendocrine action (MAGNESIUM + ASHWAGANDHA..., 2026)
Ashwagandha (*Withania somnifera*)/ Melatonin	Modulation of the stress response, sleep, and oxidative balance; possible indirect influence on triggering emotional factors.	No direct evidence exists; hypothesis based on stress-related mechanisms (MELATONIN, ASHWAGANDHA..., 2025)
Melatonin and omega-3	Antioxidant action, modulation of oxidative stress, protection of connexin 43, reduction of myocardial fibrosis, and antiarrhythmic effects in catecholaminergic stress models.	Preclinical evidence demonstrates cardioprotective effects in animal models subjected to catecholamine overload; possible translational relevance to mechanisms involved in Turner syndrome, but without direct clinical evidence in the syndrome (BACOVA et al., 2020).
Quercetin and *Salvia miltiorrhiza* (Danshen)	Antioxidant and anti-inflammatory activity, modulation of endothelial function, reduction of oxidative stress, and possible cardiovascular protection.	Studies in coronary artery disease and ischemic heart disease suggest beneficial effects on cardiovascular function and clinical events; possible mechanistic relevance to pathways involved in ST, but without direct clinical evidence in the syndrome (GAO et al., 2020).
L-theanine	Anxiolytic action through modulation of neurotransmitters (GABA, dopamine); synergistic effect with magnesium in combined formulations.	Evidence predominantly focused on reducing general anxiety; absence of specific cardiovascular studies.

Source: *Prepared by the authors (2026), based on the sources cited in the evidence column.*

From a conceptual standpoint, the rationale for investigating natural compounds as adjuvant therapy is based on mechanisms potentially relevant to Takotsubo Syndrome, including the reduction of myocardial oxidative stress, the modulation of the psychological stress response, and the maintenance of cardiac electrophysiological stability. However, these applications remain hypothetical, since there is no direct clinical evidence to prove a therapeutic benefit of these compounds in TS (Gao et al., 2020; Mukherjee et al., 2024).

Despite the plausible pathophysiological rationale, it is crucial to highlight that none of the natural products discussed have, as of the conclusion of this review, been formally recommended in guidelines from cardiology societies for the treatment or prevention of Takotsubo Syndrome. Their use should be considered exclusively complementary, individualized, and under professional guidance, without replacing conventional evidence-based therapy (Sethi et al., 2023; Jamil et al., 2025).

The semiology of Acupuncture in Japanese and Chinese medicine, dating back approximately five thousand years, has pointed out and discussed the effects of intense emotions (whether good or bad) and their effects on the heart and other organs (Maciocia, 2006). The phyto-adaptogenic effect of certain herbal extracts that modulate the psychoneuroimmunometabolic axis is well-known in the literature. These extracts have been studied for the recovery from post-war trauma in populations still deprived of food resources, enabling them to rebuild their lives. The terpenoid class of plant chemicals is particularly noteworthy, as many of them modulate the thyroid, adrenal glands, and pancreas, in addition to their behavioral effects such as stress reduction and sleep modulation (Panossian et al., 1999). Furthermore, homeopathic medicines (medical specialty – CFM, 1980) may be used as adjuvants also aiming at reducing this oxidative stress (Varricchio, 2010; Andrade et al., 2022). Undoubtedly, prioritized nutritional guidance, focused on functional foods (Bellizzi et al., 2022).

For all these reasons discussed, which are very contemporary, investment should be made in the use of phyto-adaptogenic extracts (Varricchio, 2008), adaptogenic-like extracts, diluted by the classic Hahnemannian method such as *Cactus grandiflora*, *Arnica montana* and

Bryonia alba (Varricchio, 1995; Wasim et al., 2022; Pustiglione, 2024; Varricchio et al., 2025) and, especially, in conventional functional foods such as species of the genus Echinacea and unconventional foods, such as the aqueous extract of *Panicum maximum*, among others (Hansel-Martins et al., 2025; Gaspar et al., 2026).

The issue of exercises for cardiovascular rehabilitation and health maintenance, as well as prevention, will be discussed soon. Due to the complexity of secretion clearance, in-depth attention will be given to this topic.

DISCUSSION

Comparative synthesis of scientific production (2000–2025)

Table 6 presents a chronological summary of the most relevant scientific milestones on Takotsubo Syndrome, highlighting the evolution of knowledge between the years 2000 and 2025, from initial international recognition to the consolidation of validated diagnostic criteria and the investigation of complementary therapies.

Table 6: Chronological milestones in scientific production on Takotsubo Syndrome (2000–2025).

Period	Scientific milestone	Main contribution
2001	Tsuchihashi et al. publish case series in an international journal	First widespread recognition of the syndrome outside of Japan.
2004–2008	Mayo Clinic Criteria (original and modified)	First widely adopted diagnostic standardization
2005	Wittstein et al. (New England Journal of Medicine)	Demonstration of hypercatecholaminemia as a pathophysiological substrate
2006–2012	Population-based epidemiological studies (USA)	Documentation of the significant increase in hospital incidence.
2008	Prasad, Lerman and Rihal (American Heart Journal)	Consolidation of the term "apical ballooning syndrome" and revised criteria.
2014–2015	ESC/Heart Failure Association Position Statement; NEJM (Templin et al.)	Recognition of anatomical variants; publication of the largest international registry (InterTAK)

Period	Scientific milestone	Main contribution
2016	Ghadri et al. (European Heart Journal)	Formal description of "Happy Heart Syndrome"
2018	International Expert Consensus Document, Parts I and II	InterTAK Diagnostic Criteria and Score; consensus-based therapeutic consolidation
2020–2022	COVID-19 pandemic	Documentation of a transient increase in incidence associated with psychosocial stress and viral infection.
2022–2025	Network meta-analyses on pharmacological therapies; validation studies of the InterTAK Score in new populations; investigation of adjuvant natural products.	Consolidation of therapeutic gaps; geographic expansion of studies (Middle East, Palestine); growing interest in complementary antioxidant approaches.

Source: Prepared by the authors (2026), based on the set of references cited in this study.

This study was limited to a theoretical review without citing integrated multicenter studies. This study contributed to the integrative update of the state of the art and its contextualization for geo-climatic emergencies that cause or evoke intense emotions through shocking images, due to the loss of loved ones and those far away, stemming from the human capacity for emotion and solidarity.

FINAL CONSIDERATIONS

This integrative systematic review comprehensively systematized the scientific knowledge produced between 2000 and 2025 on Broken Heart Syndrome, scientifically known as Takotsubo Syndrome. Significant evolution was observed in the understanding of the condition, from its initial description restricted to Japan to its recognition as an acute heart failure syndrome of global clinical relevance, predominantly affecting postmenopausal women, with a more widely documented geographic distribution in Asia, Western Europe, and North America, and increasing recognition in regions historically underrepresented in the literature, such as the Middle East and Latin America.

The circumstances surrounding the onset of the syndrome are heterogeneous, encompassing both negative emotional triggers—which gave rise to the popular term "broken

heart"—and physical triggers and, more recently, positive emotional triggers, characterizing the so-called "happy heart syndrome." Diagnostic criteria have progressively evolved over fifteen years, culminating in the InterTAK Diagnostic Score, currently the most validated instrument for differentiating between TS and acute coronary syndrome.

Regarding treatment, the lack of randomized clinical trials to support specific therapeutic approaches remains evident, with current management largely based on extrapolations from conventional heart failure guidelines. In this context, the investigated adjuvant natural products—omega-3, coenzyme Q10, magnesium, ashwagandha, melatonin, and polyphenolic compounds—present a plausible pathophysiological rationale, centered on reducing oxidative stress and modulating the neuroendocrine response to stress; however, they lack direct and specific clinical evidence for Takotsubo Syndrome, representing a promising, but still incipient, field of scientific investigation. Acupuncture is recommended as an adjuvant in improving symptoms.

For future studies, it is recommended to conduct randomized controlled clinical trials that specifically evaluate the effectiveness of conventional pharmacological interventions and adjuvant natural products in the primary and secondary prevention of the syndrome, as well as to expand multicenter registries in geographically underrepresented regions, in order to reduce underreporting and improve the overall epidemiological understanding of Broken Heart Syndrome, a relevant demand given the risks of geo-climatic accidents.

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