Brain–Heart Axis and Phenotype-Guided Care in Takotsubo Syndrome: A Contemporary Clinical Review

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Abstract: More and more evidence suggests that Takotsubo syndrome (TTS) is not a one-size-fits-all benign self-limiting condition, but a highly heterogeneous acute heart failure syndrome. Most existing reviews are largely descriptive and fail to truly link brain–heart axis mechanisms, diagnostic refinement, and phenotype-guided care. This review focuses on recent advances since 2019, with emphasis on autonomic imbalance, neurocardiac vulnerability, multimodal imaging, Mayo and InterTAK diagnostic frameworks, and emerging contexts such as COVID-19, immune checkpoint inhibitors, and spontaneous coronary artery dissection. Current evidence points to sympathetic activation, insufficient parasympathetic regulation, coronary microvascular dysfunction, and inflammatory–immune responses jointly contributing to reversible myocardial stunning. Diagnosis cannot rely solely on ruling out obstructive coronary artery disease, because TTS can coexist with coronary artery disease, acute coronary syndrome (ACS), or SCAD. CMR and, in selected stable patients, CCTA provide useful complementary information for differential diagnosis and risk assessment. Management remains largely supportive, but stratifying patients according to hemodynamic status, left ventricular outflow tract obstruction, arrhythmic and thromboembolic risks, trigger context, and extracardiac comorbidities can make acute and long-term care more individualized. Finally, we propose a phenotype-guided clinical framework and highlight priorities for future prospective studies.

***Keywords*:** Takotsubo syndrome; stress-induced cardiomyopathy; brain–heart axis; immune checkpoint inhibitors; COVID-19; spontaneous coronary artery dissection

1. Introduction

TTS is an acute heart failure syndrome marked by transient left ventricular dysfunction. Its presentation closely resembles that of ACS, often with chest pain, elevated cardiac biomarkers, and ST-segment elevation, but coronary angiography usually finds no culprit lesion that fully accounts for the extent and distribution of wall-motion abnormalities [1,2]. In patients with a myocardial infarction with non-obstructive coronary arteries (MINOCA)-like picture, TTS is an important differential diagnosis and may also overlap with it [3]. Current diagnostic and risk stratification approaches rely heavily on exclusion, and highly specific biomarkers or imaging markers are still lacking [4]. TTS was once considered rare, self-limiting, and prognostically favorable, but recent multicenter registry studies and prognostic reviews have reported clinically relevant acute complications, an in-hospital mortality around 4%–5%, and recurrence during follow-up [5,6]. These findings make it difficult to simply label TTS as a "benign cardiomyopathy."

Epidemiological data show marked heterogeneity across regions and healthcare systems [5,7]. Postmenopausal women account for over 89% of cases [8]. Although men are less frequently affected, they face significantly higher risks of in-hospital all-cause death and serious complications [9,10]. The trigger spectrum is also expanding: beyond classic emotional and physical stressors, iatrogenic factors, neurological disorders, COVID-19 infection and vaccination, and overlaps with other non-atherosclerotic coronary syndromes have been identified [11,12]. A growing body of data suggests that chronic stress-related factors—such as sleep disturbances and persistent negative emotions—may increase susceptibility and trigger risk in some patients [13,14].

Against this background, we integrate recent TTS evidence from the perspective of brain–heart axis dysregulation and phenotype-guided management, focusing on three questions: first, how autonomic imbalance and neurocardiac vulnerability explain different triggers and outcomes; second, how to optimize diagnosis using Mayo criteria, InterTAK criteria, CMR, CCTA, and biomarker patterns to better distinguish ACS, myocarditis, MINOCA, and SCAD; and third, how to perform risk-stratified management based on hemodynamics, imaging phenotype, arrhythmic risk, thromboembolic risk, and extracardiac comorbidities.

2. Literature Search Strategy and Selection Criteria

We searched PubMed, Web of Science, and Embase for literature published between January 2019 and March 2026, using keywords including Takotsubo syndrome, stress cardiomyopathy, brain–heart axis, autonomic dysfunction, InterTAK, Mayo criteria, cardiac magnetic resonance, coronary computed tomography angiography, COVID-19, immune checkpoint inhibitor, and spontaneous coronary artery dissection. Priority was given to international consensus documents, systematic reviews, registry studies, large observational cohorts, and clinically relevant case series. Key consensus documents and diagnostic criteria published before 2019 were also included when essential for understanding current diagnostic frameworks. Articles not directly related to TTS, lacking clinical or mechanistic value, or merely repeating old concepts without new evidence were excluded. Reference lists of key articles were manually screened for additional studies. Final inclusion was based on clinical relevance, methodological quality, recency, and alignment with the three themes of brain–heart axis mechanisms, diagnostic refinement, and phenotype-guided management. As this is a focused narrative review, no quantitative synthesis or formal bias assessment was performed.

3. Epidemiological Characteristics and Clinical Features

TTS shows substantial heterogeneity in incidence and clinical presentation across populations and often coexists with multiple other conditions [7]. Demographically, postmenopausal women account for over 89% of cases [8]. Men, though less often affected, have significantly higher risks of in-hospital all-cause death, cardiogenic shock, malignant arrhythmias, and acute kidney injury [9,10]. Mean age at onset is postmenopausal, but the composition varies by trigger: exogenous catecholamine-triggered TTS is more common in younger and middle-aged individuals, whereas TTS associated with neurological or psychiatric disorders is more frequent in older patients, suggesting that younger people may also face elevated risk under specific stress conditions [15].

Race and social determinants also influence TTS. Observational analyses suggest that outcomes vary by race, ethnicity, healthcare access, and socioeconomic factors—for example, higher rates of acute kidney injury or mechanical ventilation in some groups, and increased in-hospital mortality among Hispanic patients during COVID-19 [16].

Clinically, TTS often presents with chest pain and dyspnea and is easily mistaken for ACS. ECG may show ST-segment elevation or T-wave inversion, along with elevated cardiac enzymes, but coronary angiography reveals no corresponding obstructive lesions [1,2]. Typical imaging shows apical ballooning, but there are also mid-ventricular, basal (reverse TTS), and focal variants [11]. Biventricular involvement has been reported and may be linked to adverse outcomes such as cardiogenic shock and heart failure hospitalization [17]. Regarding comorbidities, psychiatric disorders (e.g., anxiety and depression) are overrepresented in TTS patients, suggesting that chronic stress and affective dysregulation may increase susceptibility [18,19]. Autoimmune diseases, malignancies, neurological disorders, and cardiovascular risk factors such as hypertension frequently coexist with TTS and significantly affect disease course and long-term prognosis [11,20]. Table 1 summarizes contemporary epidemiological and prognostic evidence, highlighting heterogeneity across sex, triggers, comorbidities, recurrence, and emerging contexts.

Table 1. Contemporary evidence on epidemiology and prognosis in Takotsubo syndrome

Evidence domain	Representative evidence	Main finding	Clinical relevance
Overall epidemiology	InterTAK Registry [5]	TTS predominantly affects postmenopausal women but remains clinically heterogeneous.	TTS should not be viewed as a single uniform phenotype.
Short-term prognosis	Registry and cohort studies [7]	In-hospital mortality is approximately 4%–5%, with frequent acute complications.	Acute-phase monitoring and risk stratification are essential.
Sex differences	Meta-analyses and sex-focused reviews [9,10]	Women are more frequently affected, whereas men have worse short-term outcomes.	Male sex should be considered a high-risk feature.
Recurrence	Long-term observational studies [6,21]	Recurrence occurs in a minority of patients and may show different ballooning patterns.	Structured follow-up is needed even after ventricular recovery.
Trigger-related heterogeneity	Reviews of emotional, physical, neurological, and iatrogenic triggers [11,15]	Physical and neurological triggers are often associated with more severe clinical courses.	Trigger context may guide risk assessment.
Racial and social disparities	Observational analyses [16]	Outcomes may vary by race, ethnicity, healthcare access, and socioeconomic factors.	Non-biological determinants should be considered in prognosis.
COVID-19 context	COVID-19-era reviews and reports [22]	Inflammation, hypoxemia, and pandemic stress may contribute to TTS occurrence.	COVID-19-associated TTS should be treated as a high-risk context.
SCAD overlap	Contemporary reviews and case-based evidence [11]	TTS may coexist with or mimic SCAD, increasing diagnostic uncertainty.	Multimodal imaging is important in suspected overlap states.
Thromboembolic risk	Reviews of thromboembolic complications [23]	Severe apical akinesia and reduced LVEF increase LV thrombus and embolic risk.	Anticoagulation should be individualized in high-risk patients.

Abbreviations: TTS, Takotsubo syndrome; SCAD, spontaneous coronary artery dissection; LVEF, left ventricular ejection fraction; LV, left ventricular. Overall, these findings support a shift from descriptive epidemiology toward phenotype-informed risk stratification.

4. Specific Disease States and Related Cardiovascular Events

In certain clinical settings, the risk of TTS is markedly increased [11]. Neurological disorders are particularly prominent, including status epilepticus, subarachnoid hemorrhage, ischemic stroke, and traumatic brain injury [24,25]. These conditions can profoundly disrupt the brain–heart axis, triggering sympathetic storms and TTS [24,25]. Malignancy and treatment-related chronic psychological and physiological stress are also important triggers; in some patients, concurrent chemotherapy, radiotherapy, or immune checkpoint inhibitor (ICI) therapy further complicates management [11]. Endocrine disturbances—such as pheochromocytoma, hyperthyroidism, and severe hyponatremia—can induce TTS through sustained or abrupt catecholamine elevation and metabolic dysregulation [15].

During the COVID-19 pandemic, TTS has been reported in association with both infection-related physical stress and pandemic-related emotional stress. Therefore, COVID-19-associated TTS should be interpreted as a clinically important stress-related context rather than as a distinct mechanistic subtype.[22] Spontaneous coronary artery dissection (SCAD) is an important cause of non-atherosclerotic myocardial infarction in young women and has been reported to coexist with or mimic TTS, increasing diagnostic and therapeutic complexity in overlap presentations.[11] For patients with suspected overlap, intensified imaging surveillance is warranted, and anticoagulation and antiplatelet strategies should be carefully balanced based on individualized thrombotic and bleeding risks . Taken together, these clinical contexts should not be interpreted as entirely separate disease entities, but rather as important stress environments that may unmask neurocardiac vulnerability and influence diagnostic and therapeutic decisions.

5. Core Pathophysiological Mechanisms

The development of TTS can be summarized as follows: emotional or physical stressors activate the brain–heart axis, leading to excessive sympathetic activation and a surge of catecholamines, which act synergistically through direct myocardial toxicity, coronary microvascular dysfunction, and inflammatory–immune dysregulation, ultimately resulting in reversible left ventricular dysfunction (Figure1). Sympathetic activation and acute catecholamine elevation are key initiating events; downstream effects include intracellular calcium overload, oxidative stress, mitochondrial dysfunction, microvascular constriction, and supply–demand mismatch [15,24]. The relatively higher β-adrenergic receptor sensitivity of the apical myocardium has been proposed as one explanation for the classic apical ballooning pattern [24].

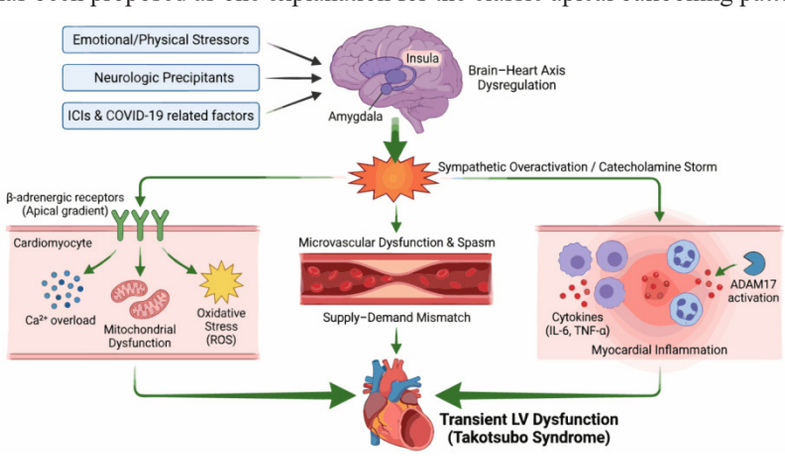

Figure 1. Schematic illustration of the brain–heart axis and sympathetic–inflammatory mechanisms in Takotsubo syndrome

Inflammation and immune modulation also play important roles. Infiltration and phenotypic changes of macrophages and neutrophils in myocardial tissue suggest that local immune imbalance contributes to functional impairment. In infection-associated cases, cytokine activation and inflammatory–metabolic pathways may further influence myocardial injury and recovery [22,24]. Upstream, brain regions such as the insula and amygdala are central to stress signal perception and processing; acute insults like stroke, subarachnoid hemorrhage, or severe psychological trauma can lead to profound autonomic imbalance and sympathetic storms [24,25].

HRV-based evidence supports sustained autonomic imbalance in TTS, characterized by enhanced sympathetic

activation and reduced parasympathetic/vagal modulation[26]. These findings suggest that brain–heart axis dysfunction in TTS extends beyond sympathetic overactivation, although the causal contribution of impaired vagal regulation to myocardial stunning, coronary microvascular dysfunction, electrical instability, and inflammation remains to be clarified. Future studies integrating heart-rate variability, autonomic function testing, neuroimaging, and circulating inflammatory biomarkers may help determine whether impaired vagal modulation represents a susceptibility marker, a severity modifier, or a potential therapeutic target in TTS.

6. Diagnostic Strategies and Differential Diagnosis

6.1 Diagnostic Approach and Criteria

Current diagnosis of TTS should move beyond a purely exclusion-based approach. The revised Mayo Clinic criteria and the InterTAK Diagnostic Criteria remain the most widely referenced frameworks, but contemporary interpretation emphasizes integrating clinical presentation, trigger context, ECG evolution, biomarker patterns, coronary anatomy, and wall-motion abnormalities [27,28]. The presence of obstructive coronary artery disease should not be an absolute exclusion criterion. Rather, coronary lesions should be interpreted in relation to the distribution and extent of ventricular dysfunction, because TTS may coexist with CAD, ACS, or SCAD [28]. The InterTAK Diagnostic Score provides a practical adjunct for early differentiation between TTS and ACS using seven variables: female sex, emotional or physical trigger, absence of ST-segment depression, psychiatric or neurological disorder, and QTc prolongation [29]. However, it should support rather than replace coronary evaluation and multimodal imaging when ACS remains clinically plausible. Table 2 summarizes the major diagnostic frameworks and assessment tools.

Table 2. Diagnostic criteria and multimodal assessment tools for Takotsubo syndrome

Criteria / tool	Main role	Key contribution	Important limitations or notes
Mayo Clinic criteria	Historical diagnostic framework	Defines transient LV wall-motion abnormality, ACS-like presentation, modest biomarker change, and exclusion of alternative diagnoses. [27]	Useful reference framework, but relatively exclusion-based and less flexible for CAD coexistence.
InterTAK Diagnostic Criteria	Contemporary diagnostic framework	Recognizes typical and atypical ballooning patterns, RV involvement, neurological triggers, and possible coexistence of CAD. [28]	Requires integrated interpretation of coronary anatomy, wall-motion pattern, biomarkers, and imaging.
InterTAK Diagnostic Score	Early differentiation from ACS	Uses seven variables: female sex, emotional/physical trigger, absence of ST depression, psychiatric/neurological disease, and QTc prolongation. [29]	Adjunctive probability tool; it should not replace coronary evaluation when ACS is suspected.
ECG and biomarkers	Initial assessment and risk signals	ST-segment changes, T-wave inversion, QTc prolongation, modest troponin rise, and higher BNP/NT-proBNP may support suspicion. [2,4]	Not specific; serial assessment is needed and findings may overlap with ACS or myocarditis.
Echocardiography	Bedside phenotyping	Rapidly identifies ballooning pattern, LVEF, RV involvement, LVOTO, mitral regurgitation, and LV thrombus. [1]	Operator-dependent; limited tissue characterization.
Coronary angiography	Coronary assessment in ACS-like presentation	Identifies culprit coronary lesions, SCAD, plaque rupture, or coexisting CAD; ventriculography may show characteristic wall-motion patterns. [2,28]	Invasive; CAD may coexist with TTS and should not be treated as an automatic exclusion.
CMR	Tissue characterization and differential diagnosis	Detects myocardial edema and LGE patterns, helping distinguish TTS from myocardial infarction and myocarditis. [1,28]	Availability, timing, renal function, devices, and patient stability may limit use.
CCTA	Selected non-invasive coronary assessment	May assess coronary anatomy in stable patients with low-to-intermediate ACS probability or recurrent symptoms requiring reassessment. [2,28]	Not appropriate for unstable high-risk ACS; limited tissue characterization.
OCT / IVUS	Clarification of occult coronary pathology	Can detect subtle plaque rupture, erosion, intramural hematoma, or dissection when angiography is equivocal. [2]	Invasive and generally reserved for selected diagnostic dilemmas.

Abbreviations: TTS, Takotsubo syndrome; ACS, acute coronary syndrome; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CMR, cardiac magnetic resonance; ECG, electrocardiography; IVUS, intravascular ultrasound; LGE, late gadolinium enhancement; LV, left ventricular; LVEF, left ventricular ejection fraction; LVOTO, left ventricular outflow tract obstruction; OCT, optical coherence tomography; RV, right ventricular; SCAD, spontaneous coronary artery dissection. Overall, diagnosis should rely on integrated clinical, coronary, functional, and tissue-level assessment.

6.2 Biomarkers and Electrocardiography

Most TTS patients have some degree of troponin elevation, but the peak and rise kinetics are often disproportionate to the extent of wall-motion abnormalities [4]. In contrast, BNP or NT-proBNP levels are typically more markedly elevated, and

combined assessment with troponin and CK-MB can improve discrimination from ACS [4]. Common ECG abnormalities include ST-segment elevation or T-wave inversion. Early findings may mimic STEMI; however, in TTS, ST elevation often lacks corresponding reciprocal ST depression and typical pathological Q waves. During the course, diffuse, symmetric deep T-wave inversions and QTc prolongation frequently occur, warranting intensified monitoring in the acute phase [1,2].

6.3 Imaging Evaluation and Differential Diagnosis

Coronary angiography should not be just an exclusionary test—it is key to identifying culprit lesions and assessing possible coexistence of CAD or SCAD. For clinically unstable patients or those with a high probability of ACS, coronary angiography remains a necessary step [2,28]. Transthoracic echocardiography is the preferred bedside imaging tool, rapidly identifying ballooning patterns, LVEF, RV involvement, LVOTO, mitral regurgitation, and intracardiac thrombus [1]. CMR excels at tissue characterization and distinguishing TTS from myocardial infarction and myocarditis: typical findings include myocardial edema corresponding to wall-motion abnormalities, usually without transmural or subendocardial late gadolinium enhancement [1,28]. In stable patients with low-to-intermediate ACS probability or recurrent symptoms needing reassessment, CCTA can be used; in diagnostic dilemmas, OCT or IVUS may be considered to clarify subtle plaque rupture, intramural hematoma, or dissection [2,28]. Figure 2 presents a simplified phenotype-guided clinical framework.

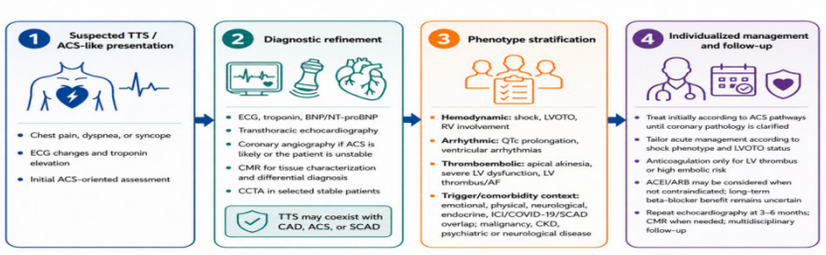

Figure 2. Simplified phenotype-guided clinical framework for Takotsubo syndrome.

(Note: ACS, acute coronary syndrome; AF, atrial fibrillation; BNP, brain natriuretic peptide; CAD, coronary artery disease; CCTA, coronary computed tomography angiography; CKD, chronic kidney disease; CMR, cardiac magnetic resonance; ICI, immune checkpoint inhibitor; LV, left ventricular; LVOTO, left ventricular outflow tract obstruction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; RV, right ventricular; SCAD, spontaneous coronary artery dissection; TTS, Takotsubo syndrome)

7. Clinical Management and Therapeutic Advances

To date, no TTS-specific treatment regimen has been established based on large randomized controlled trials. Therefore, clinical management largely follows observational evidence and expert consensus, focusing on acute supportive care and complication management, followed by pharmacotherapy and structured follow-up during recovery [7].

7.1 Acute Support, Complication Management, and Mechanical Circulatory Support

Patients with suspected TTS should be managed under continuous ECG monitoring, and initial treatment generally follows ACS protocols until coronary pathology is clarified [1,2]. Cardiogenic shock is one of the most serious complications, and management depends on whether left ventricular outflow tract obstruction is present. Without significant obstruction, inotropes such as dobutamine may be used cautiously under close monitoring. With marked obstruction, inotropes should be avoided; instead, moderate fluid resuscitation, β-blockers, and vasopressors may be used to reduce obstruction and maintain perfusion. For refractory cardiogenic shock unresponsive to pharmacotherapy, mechanical circulatory support may be considered in experienced centers as a bridge to recovery [7]. Severe apical akinesia with markedly reduced LVEF increases the risk of LV thrombus and systemic embolism; short-term anticoagulation is generally reserved for patients with confirmed thrombus or high-risk features [23]. The choice of mechanical circulatory support should be individualized based on LVOTO status, ventricular involvement, hemodynamic profile, and local expertise.

7.2 Pharmacotherapy and Follow-up

Evidence for long-term pharmacotherapy is limited and inconsistent[7]. β-blockers theoretically reduce sympathetic activity and control heart rate, but current evidence does not support their routine long-term use solely for recurrence prevention[24]. Observational studies have more consistently shown that ACEI/ARB improve long-term survival. When not contraindicated, continuation of ACEI/ARB for at least 3–6 months during recovery is suggested, with subsequent

adjustment based on left ventricular function [7]. In most patients, LVEF recovers significantly within weeks to 3 months, and repeat echocardiography at 3–6 months can help guide medication tapering and long-term management [1,7].

8. Prognosis, Complications, and Recurrence Risk

8.1 Short-term Outcomes and In-hospital Complications

Short-term outcomes in TTS are not uniformly favorable. Overall in-hospital mortality is approximately 4%–5%, comparable to some ACS cohorts, and acute complications occur in up to about 40% of patients[5,7]. Common complications include acute heart failure, cardiogenic shock, malignant ventricular arrhythmias, LVOTO, acute mitral regurgitation, intracardiac thrombus with systemic embolism, and rarely, cardiac rupture and sudden cardiac death[5,23]. Male patients, those with predominantly physical triggers, and those with malignancy or COVID-19 infection generally have worse prognoses and require more intensive monitoring and comprehensive acute management [8,22].

8.2 Long-term Outcomes, Recurrence, and Subclinical TTS

Long-term follow-up studies indicate that increased overall mortality in TTS is largely driven by non-cardiovascular causes, highlighting the central role of comorbidity burden in determining long-term outcomes[5,16]. Malignancy, chronic kidney disease, neurological disorders, and psychiatric conditions are strongly associated with adverse long-term prognosis, suggesting that long-term care should extend beyond cardiac management to include comorbidity control and psychological support [7,19]. TTS has a propensity for recurrence, with an annual rate of approximately 1%–3.5%; recurrence can occur years to decades after the initial episode, and the ballooning pattern may differ from the index event [6,21]. Limited data suggest that female sex, low body mass index, and mid-ventricular ballooning may be associated with higher recurrence risk, while the preventive effects of ACEI/ARB and β-blockers remain incompletely defined [6,7].

Emerging perspectives suggest that subclinical TTS events may share certain pathways with SCAD and exert mutual long-term influences[11]. Therefore, for high-risk individuals with a history of TTS or SCAD and multiple cardiovascular risk factors, strengthened long-term follow-up is recommended, incorporating symptom assessment and imaging (echocardiography/CMR) to facilitate early detection of potential subclinical events and recurrence risk [1].

9. Discussion

TTS is increasingly recognized as a highly heterogeneous acute heart failure syndrome rather than a benign self-limiting cardiomyopathy, but the field remains challenged by multiple competing explanatory frameworks and unresolved clinical dilemmas[3,24]. The long-standing “catecholamine toxicity” view coexists with an integrative brain–heart axis paradigm in which autonomic imbalance, microvascular dysfunction, and inflammatory–immune responses jointly determine phenotype and severity. Related debates include whether microvascular ischemia or primary myocardial stunning dominates in typical presentations, and how to interpret overlaps with MINOCA, myocarditis-like injury, and SCAD[2,11]. These controversies reflect fundamental conceptual issues regarding disease definition, trigger biology, and which features should anchor clinically actionable risk models (hemodynamics, electrical instability, thromboembolic propensity, and extracardiac comorbidity burden)[5,23]. Therefore, contemporary diagnosis should be an integrative process rather than sequential exclusion of ACS, myocarditis, and other conditions.

Current evidence has clear limitations: lack of randomized trials, inconsistent phenotyping and endpoint definitions in registries, absence of highly specific biomarkers, underpowered data in emerging contexts, and inadequate characterization of longer-term sequelae beyond LVEF recovery[4,5]. Future progress will likely depend on phenotype-informed frameworks that operationalize trigger context and neurocardiac vulnerability, diagnostic algorithms integrating standardized echocardiography/CMR with mechanism-aligned biomarker panels, and stratified or adaptive trials enriched for high-risk endotypes[4]. Because long-term outcomes are often driven by non-cardiovascular comorbidities, multidisciplinary follow-up models—linking cardiology with neurology, oncology, endocrinology, and mental health care—may represent the most immediate, high-yield step toward individualized management while mechanistic and trial evidence continues to mature [7,19].

In summary, current evidence supports mechanism-aware phenotyping, while observations at the interface of autonomic, neurological, immune, and arrhythmic disorders remain hypothesis-generating[26]. Recognizing that multiple stressors can converge and interact in clinical practice may help explain heterogeneous presentations and support more tailored prevention and follow-up strategies [30].

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