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Beyond Broken Hearts: The Promise and Limitations of Beta-blockers and Renin-angiotensin System Inhibitors for Takotsubo Syndrome

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Take Home Messages

- Takotsubo syndrome carries significant long-term risk, including high rates of mortality, major adverse cardiovascular events and recurrence, highlighting the importance for ongoing therapy.
- Renin-angiotensin system inhibitors and beta-blockers have the strongest evidence-base and are associated with better long-term survival although data on the impact on recurrence rates is limited.
- High-quality randomised controlled trials are urgently needed to guide chronic pharmacotherapy.
- Emerging anti-inflammatory and immune-targeted therapies (e.g. colchicine) show promising early signals and may shape future personalised treatment strategies.

Background

Takotsubo syndrome (TTS), also known as stress-induced cardiomyopathy or broken heart syndrome, represents approximately 1-3% of all acute coronary syndrome (ACS) presentations and up to 6% of ACS presentations in women (1,2,3). Its in-hospital mortality is comparable to that of acute ST-elevation myocardial infarction, and the risk does not end with the initial event (1,4,5,6). Long-term follow-up studies report all-cause mortality rates of approximately 5.6% per patient-year and major adverse cardiac and cerebrovascular event rates approaching 10% per patient-year (1), with recurrence occurring in 11–14% of patients within five years of the index event (7,8).

The exact mechanisms underpinning TTS are not completely understood. Although traditionally attributed to catecholamine-mediated myocardial stunning, emerging evidence points to a far more complex pathophysiology involving oestrogen deficiency, altered β_2-adrenergic receptor signalling, genetic predisposition, neuropsychiatric elements, nitrosative stress, disrupted myocardial energetics, inflammation and microvascular dysfunction (9). This expanding

mechanistic framework has stimulated growing interest in long-term pharmacotherapies to improve outcomes beyond the acute phase of the syndrome.

Role of Beta-blockers and Angiotensin Converting Enzyme Inhibitors in Long Term Pharmacotherapy

While acute care appropriately centres on haemodynamic stabilisation, long-term pharmacotherapy for TTS continues to be largely empirical and remains grounded in conventional heart-failure regimens. The guidance on chronic therapy after the index event is informed by observational cohorts and international registries, most notably the Spanish RETAKO (10) and InterTAK (11) registries representing a combined cohort of over 3,000 TTS patients with transient left ventricular dysfunction extending beyond a single coronary artery territory on echocardiogram, absence of culprit obstructive coronary disease or acute plaque rupture and new ECG changes or troponin elevation. Collectively, these datasets suggest that conventional heart-failure therapies, particularly Angiotensin converting enzyme inhibitor (ACE-i)/Angiotensin receptor blocker (ARB) and beta-blockers, are associated with improved long-term survival, although their impact on recurrence remains less certain (1,10,11).

Additionally, a meta-regression analysis of 20 non-randomized studies by Brunetti et al. hypothesized a reverse correlation between the combined use of β-blockers and ACEi/ARBs and TTS recurrence rates, raising the possibility that patients receiving combination therapy may be less likely to experience future recurrence (12).

Data from the GEIST Registry

The German-Italian-Spanish Takotsubo (GEIST) Registry is a large, multicentre observational study (over 2,800 patients) investigating long-term outcomes and medical therapy in patients with confirmed TTS across European tertiary centres between 2006 and 2022 with the median follow up of 31 months (13). Median age was 70 years, with a female predominance (≈ 85 %) and classical apical ballooning pattern on transthoracic echocardiogram in most cases (14). Older age, male sex, lower left ventricular ejection fraction (LVEF) at admission, history of neurological disorders,

presence of physical triggers, diabetes, and malignancy were predictors of recovery of ventricular function (15).

• Beta-Blocker Therapy: Among 2,125 patients (≈ 75 %) discharged on β-blockers, the median follow-up was 2.6 years. β-blocker use was associated with a significant reduction in all-cause mortality compared with no β-blocker therapy (HR 0.71; 95 % CI 0.55–0.90;P=0.006), but no significant reduction in recurrence (HR 0.74; 95 % CI 0.61–1.89) (16).

• ACE-i / ARBs: Long term use of RASi (renin-angiotensin system inhibitors) were associated with improved survival overall, but this was only statistically significant in those with admission LVEF ≤ 40%; no survival benefit was observed in those with LVEF > 40%. At long term follow-up, overall rate of TTS recurrence was 4.6% and this was not different between patients treated with RASi or not (4.8% vs 4.5% P= 0.55) (17).

The registry did not specifically evaluate the impact of combined ACEi/ARB and β-blocker therapy, so it cannot support any conclusions regarding the benefit of using both agents together in TTS.

Future directions

Although registry data consistently suggests a survival benefit with conventional heart-failure pharmacotherapy in TTS, robust randomised trials are still lacking, leaving important uncertainties in long-term management. Ongoing randomised studies such as β-TAKO trial evaluating β-blockers versus placebo for 12 months to determine effects on mortality and recurrence, are expected to guide future treatment algorithms (18).

In parallel, interest in inflammation-targeted therapy is growing. A large propensity-matched prospective cohort study of more than 2,000 patients showed that colchicine use of 1 year in TTS was associated with lower mortality and fewer cardiovascular events at 12 months (19), reinforcing the rationale for exploring anti-inflammatory agents as potential modulators for TTS recovery and recurrence.

Future strategies may include biomarker-guided therapy, using cytokine profiling and cardiac imaging (CMR, PET) to identify "immune-active" TTS phenotypes most likely to benefit from such targeted approaches (Figure).

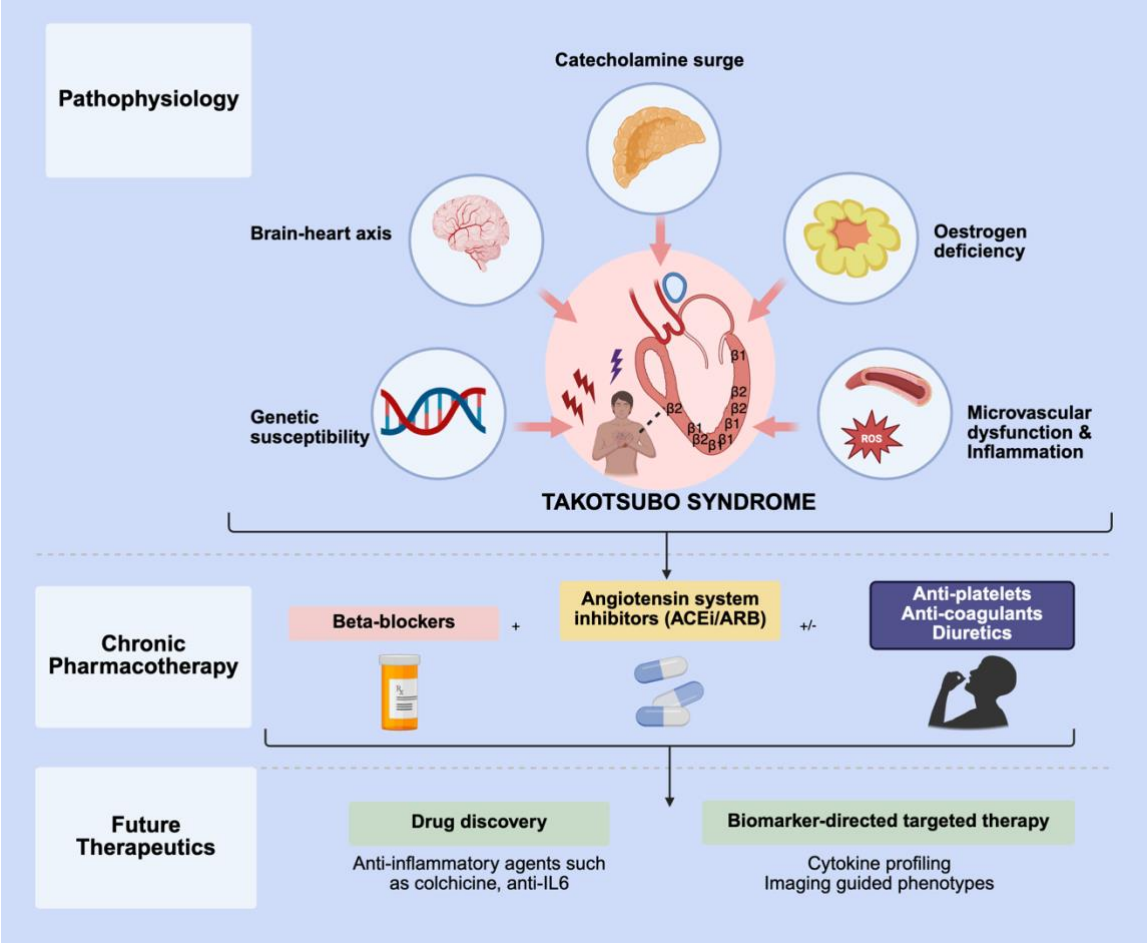

Figure 1. Takotsubo syndrome: mechanisms, current long-term pharmacotherapy and future directions. This is an original figure created with Biorender.com.

(β1 = beta-1 adrenergic receptor, β2 = Beta -2 adrenergic receptor, ACE-i = Angiotensin-converting enzyme inhibitor, ARB = Angiotensin II receptor blocker, Anti-IL6 = Anti-interleukin 6)

Conclusions

The data from the GEIST Registry therefore provides arguably the strongest real-world evidence to date supporting ACEi/ARB therapy as the cornerstone of chronic pharmacological management in TTS, with β-blockers offering additive survival benefit but no proven protection against recurrence. Nonetheless, robust randomised controlled trials are urgently required to consolidate these observational findings and to define evidence-based strategies for long-term pharmacotherapy in TTS.

Disclosures

None to declare.

References

1. Templin C, Ghadri JR, Diekmann J, Napp LC, Bataiosu DR, Jaguszewski M, Cammann VL, Sarcon A, Geyer V, Neumann CA, et al. Clinical features and outcomes of takotsubo (stress) cardiomyopathy. *N Engl J Med.* 2015;373:929–38. doi:10.1056/NEJMoa1406761
2. Akashi YJ, Goldstein DS, Barbaro G, Ueyama T. Takotsubo cardiomyopathy: a new form of acute, reversible heart failure. *Circulation.* 2008;118:2754–62. doi:10.1161/CIRCULATIONAHA.108.767012
3. Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, Cammann VL, Crea F, Galiuto L, Desmet W, et al. International expert consensus document on takotsubo syndrome (part I): clinical characteristics, diagnostic criteria, and pathophysiology. *Eur Heart J.* 2018;39:2032–46. doi:10.1093/eurheartj/ehy076
4. Uribarri A, Núñez-Gil IJ, Conty DA, Vedia O, Almendro-Delia M, Duran Cambra A, Martin-Garcia AC, Barrionuevo-Sánchez M, Martínez-Sellés M, Raposeiras-Roubín S, et al. Short- and long-term prognosis of patients with takotsubo syndrome based on different triggers: importance of the physical nature. *J Am Heart Assoc.* 2019;8:e013701. doi:10.1161/JAHA.119.013701
5. Ghadri JR, Kato K, Cammann VL, Gili S, Jurisic S, Di Vece D, Candreva A, Ding KJ, Micek J, Szawan KA, et al. Long-term prognosis of patients with takotsubo syndrome. *J Am Coll Cardiol.* 2018;72:874–82. doi:10.1016/j.jacc.2018.06.016
6. Redfors B, Jha S, Thorleifsson S, Jernberg T, Angerås O, Frobert O, Petursson P, Tornvall P, Sarno G, Ekenbäck C, et al. Short- and long-term clinical outcomes for patients with takotsubo syndrome and patients with myocardial infarction: a report from the Swedish Coronary Angiography and Angioplasty Registry. *J Am Heart Assoc.* 2021;10:e017290. doi:10.1161/JAHA.119.017290
7. El-Battrawy I, Santoro F, Stiermaier T, Möller C, Guastafierro F, Novo G, Novo S, Mariano E, Romeo F, Romeo F, et al. Incidence and clinical impact of recurrent takotsubo syndrome: results from the GEIST Registry. *J Am Heart Assoc.* 2019;8:e010753. doi:10.1161/JAHA.118.010753

8. Ghadri JR, Wittstein IS, Prasad A, Sharkey S, Dote K, Akashi YJ, Cammann VL, Crea F, Galiuto L, Desmet W, et al. International expert consensus document on takotsubo syndrome (part II): diagnostic workup, outcome, and management. *EurHeart J.* 2018;39:2047–62. doi:10.1093/eurheartj/ehy077
9. Omerovic E, Redfors B. Takotsubo syndrome: pathophysiological insights and innovations in patient care. *Nat Rev Cardiol.* 2025 Oct 2:1–6. doi:10.1038/s41569-025-01051-0
10. Almendro-Delia M, Núñez-Gil IJ, Lobo M, Andrés M, Vedia O, Sionis A, et al. Short- and long-term prognostic relevance of cardiogenic shock in takotsubo syndrome: results from the RETAKO registry. *JACC Heart Fail.* 2018;6(11):928–36. doi:10.1016/j.jchf.2018.06.015
11. Kato K, Di Vece D, Kitagawa M, Yamamoto K, Miyakoda K, Aoki S, et al. Clinical characteristics and outcomes in takotsubo syndrome: insights from the InterTAK registry. *J Cardiol.* 2025 Jan 30. doi:10.1016/j.jjcc.2025.01.006
12. Brunetti ND, Santoro F, De Gennaro L, Correale M, Gaglione A, Di Biase M, et al. Combined therapy with beta-blockers and ACE-inhibitors/angiotensin receptor blockers and recurrence of takotsubo cardiomyopathy: a meta-regression study. *Int J Cardiol.* 2017;230:281–3. doi:10.1016/j.ijcard.2016.12.040
13. ClinicalTrials.gov. The GErman Italian Spanish Takotsubo (GEIST) Registry (GEIST), Identifier: NCT04361994. Updated 2024 May 13. Available from: https://clinicaltrials.gov/study/NCT04361994
14. El-Battrawy I, Santoro F, Stiermaier T, Möller C, Guastafierro F, Novo G, et al. Incidence and clinical impact of recurrent takotsubo syndrome: results from the GEIST registry. *J Am Heart Assoc.* 2019;8(9):e010753. doi:10.1161/JAHA.118.010753
15. Pätz T, Santoro F, Cetera R, Ragnatela I, El-Battrawy I, Mezger M, Rawish E, Andrés-Villarreal M, Almendro-Delia M, Martinez-Sellés M, Uribarri A. Trigger-associated clinical implications and outcomes in Takotsubo syndrome: results from the multicenter GEIST registry. Journal of the American Heart Association. 2023 Jul 18;12(14):e028511.
16. Raposeiras-Roubin S, Santoro F, Arcari L, Vazirani R, Novo G, Uribarri A, et al. Beta-blockers and long-term mortality in takotsubo syndrome: results of the multicenter GEIST registry. *Heart Fail.* 2025;13(5):815–25.
17. Santoro F, Stiermaier T, Gil IJ, El-Battrawy I, Pätz T, Cacciotti L, et al. Renin–angiotensin system inhibitors and outcome in patients with takotsubo syndrome: a propensity score analysis of the GEIST registry. *Am Heart J.* 2024;278:127–38. doi:10.1016/j.ahj.2024.08.011
18. Alfonso F, Salamanca J, Núñez-Gil I, Ibáñez B, Sanchis J, Sabaté M, et al. Rationale and design of the beta-blockers in tako-tsubo syndrome study: a randomized clinical trial (β-Tako). *Rev Esp Cardiol (Engl Ed).* 2024 Dec 30. doi:10.1016/j.rec.2024.10.007
19. Agarwal H, Kharidia K, O'Hara P. Signals of cardioprotection with colchicine in takotsubo cardiomyopathy: a propensity-matched real-world study. *Circulation.* 2025;152(Suppl 3):A43731.