WHITE PAPER

Metabolic Intervention in Advanced Heart Failure: A Pilot Study on Trimetazidine and Rehospitalization Risk

Prepared for a pharmaceutical medical affairs / HCP-facing audience

Executive Summary

Advanced heart failure is characterized by a left ventricular ejection fraction (LVEF) below 30%. Persistent New York Heart Association (NYHA) class III-IV symptoms despite maximally tolerated guideline-directed medical therapy (GDMT), carries a high risk of hospital readmission. A 2025 systematic review and meta-analysis of 21 studies reported a pooled 30-day unplanned readmission rate of 17.7% (95% CI, 13.9%-21.5%) in chronic heart failure populations.It identified NYHA class III-IV symptoms and reduced ejection fraction as independent risk factors for readmission.[1] For many advanced HF patients, low blood pressure and impaired renal function already limit how much further conventional hemodynamic therapy such as diuretics, RAAS inhibitors, additional vasodilators, can be added, leaving few remaining pharmacological options.

This white paper summarizes a single-center, prospective, open-label pilot study conducted in Yerevan, Armenia. The study tested a different kind of intervention, trimetazidine, added to standard therapy in 40 patients with advanced HF.[2] Trimetazidine is a metabolic agent that shifts myocardial energy production from fatty acid to glucose oxidation. Over six months, the trimetazidine group showed a modest improvement in LVEF and a statistically significant reduction in E/e' ratio (a marker of left ventricular filling pressure). Other notable outcomes were fewer hospitalizations than the group on standard therapy alone. No trimetazidine-related adverse events were reported.

These results support the biological plausibility of a metabolic approach to reducing readmissions in advanced HF. However, the study's small sample, non-randomized design, single-center setting, and six-month follow-up mean the findings should be treated as hypothesis-generating rather than practice-changing. This paper outlines the evidence, the proposed mechanism, and what a confirmatory trial would need to establish before trimetazidine could be considered more broadly in this population.

The Challenge: Readmission Risk in Advanced Heart Failure

Heart failure readmissions remain one of the most persistent quality and cost problems in cardiovascular care. Currently, standard GDMT includes the combination of renin-angiotensin-system inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and SGLT2 inhibitors, now recommended as first-line treatment for heart failure with reduced ejection fraction. But evern with the guideline-directed regimen, a substantial share of patients are readmitted within 30 days of discharge. The 2025 meta-analysis cited above identified NYHA class III-IV symptoms, LVEF below 40%, chronic kidney disease, and diabetes as independent risk factors for 30-day readmission in chronic heart failure.[1]

Advanced heart failure sits at the sharper end of this risk. By definition, these are patients with LVEF under 30%, persistent NYHA III-IV symptoms despite maximal GDMT, and at least one hospitalization in the past year.[2] Many are also the patients hardest to treat further due to low systolic blood pressure, severely reduced EF, and diuretic resistance. These comorbidities are common, and further titration of hemodynamically active drugs is often limited by tolerability or renal function.[2] This creates a genuine pharmacological ceiling, a point at which the standard hemodynamic efficacy is ata limit, but the patient's risk of readmission has not gone away.

This is the clinical gap the study summarized below set out to test. Whether a treatment that works through a different mechanism entirely, myocardial energy metabolism, could offer an additional step for patients who have already reached that treatment ceiling.

Research and Evidence: A Pilot Study of Metabolic Intervention

Design and Population

This was a single-center, prospective, open-label study conducted at the "Heratsi" Hospital Complex No. 1, Yerevan State Medical University, Armenia.[2] Forty patients with advanced HF (LVEF <30%, NYHA III-IV, at least one hospitalization in the preceding 12 months) were enrolled following an index hospitalization. After discharge, patients were assigned to one of two groups: standard GDMT alone (20 patients), or standard GDMT plus trimetazidine 80 mg once daily (20 patients). Because allocation was not randomized, the study team applied propensity score analysis to help reduce selection bias between the groups.

At baseline, the two groups were broadly comparable in age (mean 65–66 years), sex distribution, prior myocardial infarction, diabetes prevalence, and baseline echocardiographic measures, including LVEF and E/e' ratio.[2]

Patients were followed for six months, with outpatient visits at 2 weeks, 1, 3, and 6 months after discharge, in addition to a baseline assessment before discharge. At each visit, clinicians assessed congestion via clinical examination and cardiovascular and lung ultrasound; echocardiographic measurements of LVEF and LV filling pressure (via tissue Doppler-derived E/e' ratio) were performed by blinded assessors according to American Society of Echocardiography and ESC Heart Failure Association guidelines.[2] Two patients in the trimetazidine group did not complete the study. One due to non-adherence, one due to death from a cardiovascular cause, leaving 38 of 40 patients (18 trimetazidine, 20 control) evaluable at six months.[2]

What the Study Found

Outcome	Trimetazidine + GDMT (n=18)	Standard GDMT alone (n=20)	Notes
LVEF, baseline → 6 months	23.7% → 25.0%	22.5% → 22.6%	Between-group change P=0.002
E/e' ratio, baseline → 6 months	15.1 → 13.7	16.78 → 16.7	Between-group change P<0.001
Patients hospitalized during follow-up	3 of 18 (16.7%)	6 of 20 (30.0%)	5 total hospitalization events (TMZ) vs 7 (control)
Hospitalization causes	5 HF decompensations	6 HF decompensations, 1 stroke	-
Deaths reported	1 (cardiovascular cause)	Not separately reported in source	Study authors describe overall 6-month mortality effect as "neutral"
Trimetazidine-related adverse events	0 reported	n/a	-
Patients requiring diuretic dose escalation / IV switch	5 of 18	7 of 20	-

Across the measured domains, the trimetazidine group showed consistent, even if modest, advantages. The improvement in LVEF was small in absolute terms; the reduction in E/e' ratio was the study's strongest statistical signal ($P<0.001$). Per the study authors, this is the first data specifically evaluating trimetazidine's effect on LV filling pressure in an advanced HF population.[2] Hospitalizations were both fewer and, by cause, less severe in the trimetazidine group. The seven hospitalizations in the control group included one stroke, while all five in the trimetazidine group were HF decompensations. No adverse events attributed to trimetazidine were reported.

Analysis: A Metabolic Lever for a Hemodynamic Problem

Why might a drug developed for angina help a filling-pressure and readmission problem in advanced HF? The proposed mechanism is metabolic rather than hemodynamic. Trimetazidine selectively inhibits mitochondrial long-chain 3-ketoacyl coenzyme. A thiolase, an enzyme involved in fatty acid oxidation, shifting the heart's energy substrate preference toward glucose oxidation.[2`3] Because glucose oxidation is thought to generate ATP with less oxygen cost than fatty acid oxidation, this shift may allow a failing, energy-starved myocardium to work more efficiently without any change in blood flow, blood pressure, or fluid status.[2] At a cellular level, trimetazidine has also been associated with protection against intracellular acidosis and sodium/calcium overload. Mechanisms proposed to protect cardiac cells from necrotic and apoptotic death also include reduced oxidative damage.[2]

This mechanism is consistent with, though distinct from, prior trimetazidine research in heart failure with reduced ejection fraction, where the drug has been associated with improved LV function and functional capacity.[2] What this pilot study adds is a specific look at LV filling pressure, a hemodynamic marker, not only a functional one, in a population with more severe, advanced disease. The authors describe this as the first study to evaluate trimetazidine's effect on LV filling pressure in advanced HF specifically.[2]

What the data do and do not show? The reduction in E/e' ratio and the numerically lower hospitalization rate are consistent with a real clinical effect, but the study was not designed or powered to establish a mortality benefit. Morepver, six months is too short a window to draw conclusions about longer-term survival. The study authors themselves describe the improvement as "moderate, but statistically evident," and explicitly note that the effect on mortality was neutral over the follow-up period.[2]

Considerations for Practice and Further Research

For a clinician managing a patient who has reached the ceiling of the standard hemodynamic medications, this data offers a plausible discussion point. A metabolic add-on with, a clean safety profile could be useful for patients with blood pressure too low, kidneys too fragile, and no room for another diuretic or vasodilator. Regardless, the study being a single-center, open-label pilot, cannot be not a basis for treating trimetazidine as standard of care in advanced HF.

Several gaps would need to close before that discussion could move further:

- Randomization. Patients in this study were allocated to treatment groups non-randomly, based on clinical judgment, with propensity score analysis used afterward to reduce selection bias. A randomized design would remove this uncertainty.
- Sample size and duration. Thirty-eight evaluable patients over six months cannot reliably assess mortality or long-term hospitalization benefit; the study's own limitations section acknowledges this directly.

- Multicenter validation. A single-center design in one health system limits how confidently the findings generalize to other populations and care settings.
- Confirmation of the filling-pressure signal. Because this is described as the first study to look at trimetazidine's effect on LV filling pressure in advanced HF, replication in an independent cohort would meaningfully strengthen the evidence base.

None of this diminishes the value of the findings, a statistically significant reduction in a hemodynamic marker, with no observed treatment-related harm, is a reasonable basis for a larger trial, not yet for a treatment recommendation.

Conclusion and Next Steps

This pilot study offers an early but coherent finding that a metabolic intervention, trimetazidine, may have a role in advanced heart failure management. Specifically by improving LV filling pressure and possibly reducing readmissions, in patients who have limited room left for further hemodynamic therapy. The proposed mechanism, a shift from fatty acid to glucose oxidation at the myocardial level, is biologically plausible and consistent with prior trimetazidine research in less severe HF populations.

The responsible next step is confirmation through an adequately powered, randomized, multicenter trial with a longer follow-up period. A study designed specifically to test whether the filling-pressure and hospitalization signals seen here translate into a durable reduction in readmissions and a mortality benefit. Until that evidence exists, trimetazidine remains an investigational add-on for this population, which is a reasonable topic for clinical discussion.

References

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3. Kantor PF, Lucien A, Kozak R, Lopaschuk GD. The antianginal drug trimetazidine shifts cardiac energy metabolism from fatty acid oxidation to glucose oxidation by inhibiting mitochondrial long-chain 3-ketoacyl coenzyme A thiolase. Circ Res. 2000;86:580–588.

For the full study methodology, statistical analysis, and complete reference list, the peer-reviewed publication is available on here my website.

Written by: Sama Shamyar, MD

Published: *30/July/2026* | **Last reviewed:** *30/July/2026*

MLR approved: … | **Valid until:** …

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Adapted by me from my own co-authored publication (Sisakian, Muradyan, Babayan, Sargsyan, Shamyar, et al., 2025, American Journal of Cardiovascular Diseases), rewritten for portfolio demonstration purposes. Structured as a healthcare white for a pharma / medical affairs audience rather than the original peer-reviewed or patient-facing formats.