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Angiotensin Receptor-Neprilysin Inhibition in Chagas Cardiomyopathy: Clinical Practice Update

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ABSTRACT

Background: Chronic Chagas cardiomyopathy is an arrhythmogenic, fibrosis-prone form of heart failure that develops years after *Trypanosoma cruzi* infection. Standard therapy has largely been extrapolated from non-Chagas trials. Angiotensin receptor-neprilysin inhibition

(ARNI) offers a biologically plausible approach by enhancing natriuretic peptide/cGMP signaling while attenuating the renin-angiotensin-aldosterone system.

Objective: To summarize contemporary evidence on ARNI for heart failure due to Chagas disease, place eplerenone within guideline-directed therapy and translate these data into a practical treatment pathway.

Methods: Narrative review informed by a targeted search of PubMed, Embase, and the Cochrane Library (January 2000–September 2025) using terms related to Chagas cardiomyopathy, sacubitril/valsartan, neprilysin, eplerenone/mineralocorticoid receptor antagonists and heart failure. English, Spanish, and Portuguese publications were considered. Randomized and observational studies, major guidelines, and congress communications for the Chagas-specific ARNI trial were included; case reports and nonclinical studies were excluded. No meta-analysis was performed.

Results: Across broad HFrEF populations, ARNI reduces clinical events and NT-proBNP. In Chagas cardiomyopathy, prior evidence was limited; the Chagas-specific randomized trial presented at a scientific congress suggests a favorable hierarchical outcome with sacubitril/valsartan versus enalapril, driven primarily by early NT-proBNP reduction, with a safety profile consistent with prior experience. Eplerenone remains a complementary therapy targeting aldosterone-related fibrosis. A practical, stepwise pathway for implementation is outlined.

Conclusions: For eligible patients with heart failure due to Chagas disease, transition to sacubitril/valsartan appears reasonable, with careful titration and routine laboratory surveillance; eplerenone represents a complementary option within complete guideline-directed therapy. Further peer-reviewed results from the Chagas-specific trial are needed to refine effect sizes and subgroup guidance.

Keywords: Chagas disease; Chagas cardiomyopathy; heart failure; sacubitril/valsartan; angiotensin receptor–neprilysin inhibition; eplerenone; mineralocorticoid receptor antagonist; NT-proBNP; arrhythmias.

Słowa kluczowe: choroba Chagasa; kardiomiopatia Chagasa; niewydolność serca; sakubitryl/walsartan; hamowanie neprylizyny i receptora angiotensyny; eplerenon; antagonista receptora mineralokortykoidowego; NT-proBNP; arytmie.

INTRODUCTION

Chagas disease (American trypanosomiasis) is an infection that remains a major cause of cardiomyopathy in Latin America and through migration, worldwide. Years after the initial *Trypanosoma cruzi* infection, many patients develop a form of heart failure marked by ventricular arrhythmias, conduction disease, and a characteristic left-ventricular apical aneurysm that raises thromboembolic risk. Outcomes are often worse than in non-Chagas heart failure at similar ejection fractions. [1–3]

The biology helps explain this clinical pattern. Low-grade parasite persistence and immune-mediated injury promote myocarditis and replacement fibrosis, microvascular dysfunction causes ischemia despite unobstructed coronaries and early autonomic denervation increases electrical instability. Together these processes create a scar-rich, arrhythmogenic myocardium that is highly susceptible to adverse remodeling. [3–8]

Therapy has long been extrapolated from broader heart-failure trials. Angiotensin receptor-neprilysin inhibition with sacubitril/valsartan is mechanistically appealing because it enhances natriuretic peptide/cGMP signaling while blocking the renin–angiotensin system - actions linked to reverse remodeling and antifibrotic effects. Large trials in general HFrEF established clinical benefits and the first randomized study focused on heart failure due to Chagas disease (PARACHUTE-HF) reported superiority over enalapril on a hierarchical composite driven by larger early NT-proBNP reduction with a familiar safety profile. Within guideline-directed care, eplerenone complements sacubitril/valsartan by countering aldosterone-mediated inflammation and interstitial fibrosis, provided potassium and renal function are closely monitored. [9–18, 19–24]

MATERIALS AND METHODS

This is a narrative (non-meta-analytic) review focused on ARNI use in heart failure due to Chagas disease and on the complementary role of eplerenone.

Search Strategy

A targeted literature search was conducted in PubMed/MEDLINE, Embase, and the Cochrane Library for publications from January 2000 to September 2025. Search terms combined free text and controlled vocabulary (MeSH/Emtree) for: *Chagas cardiomyopathy*, *Trypanosoma cruzi*, *Chagas disease*, *sacubitril/valsartan*, *neprilysin*, *angiotensin receptor–neprilysin*, *eplerenone*, *mineralocorticoid receptor antagonist*, and *heart failure*. Boolean operators

("AND", "OR") were used; filters limited results to human studies in English, Spanish, or Portuguese.

Inclusion Criteria

- Randomized or prospective studies of ARNI or eplerenone in heart failure (any etiology), with Chagas-specific data prioritized when available.
- Major practice guidelines and authoritative reviews on Chagas cardiomyopathy and heart failure therapy.
- Congress communications and design papers for the Chagas-specific ARNI trial, given the recency of results.

Exclusion Criteria

- Animal or in-vitro studies; pediatric populations.
- Case reports, narrative editorials without original data, and non-cardiac outcomes not relevant to heart failure.

Study Selection

Titles/abstracts were screened for relevance; potentially eligible full texts were reviewed against the criteria above. Data were qualitatively extracted on study design, population, interventions, comparators, outcomes (clinical events, NT-proBNP, safety), and follow-up. No quantitative synthesis was undertaken.

Quality assessment

Given the narrative scope, formal risk-of-bias scoring was not performed across all studies. For randomized trials, risk-of-bias domains (randomization, allocation concealment, blinding, missing data, selective reporting) were considered qualitatively; for observational studies, selection and confounding risks were noted. Evidence from congress reports was treated as pre-publication signal.

Synthesis

Findings were integrated thematically: (1) pathophysiology of Chagas cardiomyopathy relevant to neurohormonal therapy; (2) ARNI mechanisms and HFrEF evidence; (3) Chagas-specific ARNI signal; (4) role of eplerenone; and (5) practical implementation.

ARNI - FROM MECHANISM TO BROAD HFrEF EVIDENCE

Sacubitril/valsartan is a two-in-one heart-failure medicine. One part (sacubitril) stops an enzyme that normally breaks down the body's "helpful" heart hormones (natriuretic peptides). That lets these hormones work longer: blood vessels relax, the kidneys get rid of extra salt and

water, and the heart's muscle is less likely to thicken and scar. The other part (valsartan) blocks the angiotensin II receptor, turning down the renin-angiotensin-aldosterone system that raises blood pressure and drives harmful remodeling. Working together, these actions lower filling pressures, reduce wall stress, and support healthier reverse remodeling of the left ventricle. [9–13]

This mechanism matches the problems seen in heart failure due to Chagas disease: a scar-prone, electrically unstable myocardium with microvascular dysfunction and neurohormonal activation. In large trials of general HFrEF, sacubitril/valsartan beat enalapril for preventing cardiovascular death and heart-failure hospitalization, and it cut NT-proBNP quickly when started during or soon after decompensation. PARACHUTE-HF, the first randomized trial focused on Chagas disease, now suggests a better overall hierarchical outcome versus enalapril, mainly because NT-proBNP falls more with sacubitril/valsartan, while safety looks familiar. Together, these data support switching eligible patients from an ACE inhibitor or ARB to sacubitril/valsartan and then titrating as tolerated. [9–13, 14–18]

PARACHUTE-HF – FROM HYPOTHESIS TO FIRST RANDOMIZED SIGNAL

For years, treatment of heart failure due to Chagas disease relied on borrowing from non-Chagas trials. PARACHUTE-HF was designed to test that assumption directly. The trial compared sacubitril/valsartan with an active standard (enalapril) in adults with heart failure due to Chagas disease across multiple Latin-American centers, on top of usual care. The primary endpoint was deliberately hierarchical, reflecting what matters to patients and clinicians - cardiovascular death and heart-failure hospitalization, while also capturing short-term biological response via the percentage change in NT-proBNP at 12 weeks. This structure increased sensitivity to a treatment signal in a condition where large mortality trials are difficult to run. [14]

At the European Society of Cardiology Congress in 2025, investigators reported a statistically significant advantage of sacubitril/valsartan over enalapril for the primary composite. The advantage appears to have been driven primarily by a larger early fall in NT-proBNP with sacubitril/valsartan, whereas event rates for cardiovascular death and the first heart-failure hospitalization appeared similar between groups over the available follow-up. Tolerability and safety were consistent with prior experience, aligning with prior heart-failure. [15–18]

This result is biologically plausible given the disease biology: enhancing natriuretic-peptide/cGMP signaling while blocking the angiotensin II receptor addresses vasoconstriction, sodium retention, and fibrosis. An early NT-proBNP response does not answer every question

about hard outcomes, but it aligns with reverse-remodeling physiology and prior ARNI data. In practice, for hemodynamically stable patients with adequate blood pressure and renal function, transition from an ACE inhibitor or ARB to sacubitril/valsartan is reasonable, with low-dose initiation, careful titration, and routine checks of blood pressure, creatinine, and potassium. Adding a mineralocorticoid receptor antagonist such as eplerenone remains important to counter aldosterone-driven fibrosis. [12–13, 15–18, 19–24]

WHERE EPLERENONE FITS (AND WHY IT COMPLEMENTS ARNI)

Aldosterone promotes sodium retention, endothelial dysfunction, inflammation, and myocardial fibrosis - central processes in Chagas cardiomyopathy. MRAs are mortality-reducing across HFrEF: spironolactone in severe HFrEF (RALES), eplerenone post-MI with LV dysfunction (EPHESUS), and in mild HFrEF (EMPHASIS-HF). Population-level experience underscores hyperkalemia risk after widespread MRA adoption, mandating structured potassium/renal monitoring. Eplerenone is often preferred when endocrine adverse effects from spironolactone are problematic. [19–22]

Table 1. Therapies at a Glance in Chagas Cardiomyopathy

Therapy	**Mechanistic rationale in Chagas cardiomyopathy**	**Evidence base (Chagas-specific vs. general HFrEF)**	**Expected effects (signals/established)**	**Key safety points**
Sacubitril/valsartan (ARNI)	Enhances natriuretic peptide/cGMP signaling; AT1 blockade counters RAAS; aligns with fibrosis- and microvascular-heavy biology	Chagas-specific randomized signal (conference) suggesting advantage vs enalapril on hierarchical composite; robust outcome benefits in general HFrEF	Early NT-proBNP reduction; in HFrEF broadly, fewer CV deaths/HF hospitalizations	Hypotension, ↑K^+, renal function decline; 36-h ACEi washout; avoid after ACEi/ARNI-related

				angioedema
Eplerenone (MRA)	Blocks aldosterone-driven inflammation and interstitial fibrosis	Mortality benefit in HFrEF (RALES/EPHESUS/EMPHASIS); extrapolated to Chagas cardiomyopathy	Signals for anti-fibrotic/remodeling support; survival benefit in HFrEF broadly	Hyperkalemia, renal dysfunction; avoid strong CYP3A4 inhibitors; do not start if K^+>5.0 or eGFR<30
Evidence-based β-blocker	Anti-adrenergic, anti-arrhythmic; supports reverse remodeling	Mortality/morbidity benefit in HFrEF; extrapolated to Chagas cardiomyopathy	↓HF events and sudden death (HFrEF broadly)	Bradycardia, hypotension
SGLT2 inhibitor	Natriuretic/renal/hemodynamic benefits; metabolic neutrality	Event reduction in HFrEF irrespective of diabetes; extrapolated	↓HF hospitalization and CV death (HFrEF broadly)	Genitourinary infections, volume depletion

AT1- angiotensin II type-1 receptor; RAAS – renin-angiotensin-aldosterone system; CV - cardiovascular; HFrEF - heart failure with reduced ejection fraction.

A TREATMENT PATHWAY

Care should begin with confirmation of cause and phenotype, incorporating rhythm assessment and structural risk features and with clinical stabilization before disease modifying therapy is adjusted. [3,12,13]

In eligible patients, transition from an ACE inhibitor or ARB to sacubitril/valsartan is appropriate given guideline positioning and the randomized signal from PARACHUTE-HF.

Uptitration should proceed as tolerated, with routine safety checks embedded in follow-up, early biomarker review can help confirm treatment trajectory without substituting for clinical judgment. [12–18]

A mineralocorticoid receptor antagonist (commonly eplerenone) should be added unless contraindicated, recognizing its complementarity to angiotensin receptor–neprilysin inhibition. Completion of guideline directed therapy with an evidence-based β-blocker and an SGLT2 inhibitor remains standard, while diuretics are used to control congestion rather than to target outcomes. [12,13,19–24]

Because the myocardium in Chagas disease is scar-prone and arrhythmogenic, rhythm surveillance is warranted. Anticoagulation is indicated when thromboembolic risk is present (e.g., apical aneurysm, thrombus or atrial fibrillation). Device therapy (ICD/CRT) follows general indications, applied with attention to conduction disease and scar distribution. [3,12,13]

Follow-up should be structured: periodic assessment of symptoms and functional status, reassessment of biomarkers and renal, potassium profiles and interval imaging to track remodeling. When intolerance occurs, dose adjustment and sequencing rather than withdrawal. [12,13]

Health-system considerations matter. Access to medications and labs, simplified titration schedules, and coordinated care support durability of therapy. Future data from fully published PARACHUTE-HF outcomes will refine effect sizes and subgroup guidance, but current evidence justifies implementation now in appropriately selected patients. [14–18]

DRUG SAFETY

Coadministration of sacubitril/valsartan with an ACE inhibitor is contraindicated, a 36-hour washout is required when switching from an ACE inhibitor. Prior angioedema related to ACEi/ARNI contraindicates use and exposure during pregnancy should be avoided. For eplerenone, initiation is inappropriate when K^+ >5.0 mmol/L or eGFR <30 mL/min/1.73 m^2; concomitant strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, ritonavir) are contraindicated, and caution is warranted with other potassium-raising agents. In Chagas cardiomyopathy, where low systolic blood pressure is common, slow uptitration is advised, with diuretic adjustment as needed to limit hypotension. If hyperkalemia occurs, maintenance of therapy is preferred through dose adjustment, diuretic optimization, and use of potassium binders rather than discontinuation.

CONCLUSIONS

Chagas cardiomyopathy combines parasite-related injury, microvascular dysfunction, autonomic denervation, and patchy fibrosis to create a scar-rich, arrhythmogenic myocardium. In that context, therapies that both enhance natriuretic peptide/cGMP signaling and attenuate RAAS are biologically compelling. The Chagas-specific randomized trial presented at a scientific congress reported a statistically significant signal favoring sacubitril/valsartan over enalapril on a hierarchical composite, apparently driven by early NT-proBNP reductions with a safety profile consistent with experience in broader heart failure. While peer-reviewed outcomes will better define effects on cardiovascular death and hospitalization, the direction of evidence supports transitioning eligible patients from ACE inhibitor or ARB to sacubitril/valsartan with careful titration and routine laboratory surveillance.

Eplerenone complements ARNI by targeting aldosterone-mediated fibrosis, a central feature of the chagasic substrate and should be integrated unless contraindicated, alongside an evidence-based β-blocker and an SGLT2 inhibitor. Given frequent low systolic blood pressure, stepwise dose escalation and judicious diuretic adjustment are advisable; when hyperkalemia occurs, therapy is best maintained through dose modification and supportive measures rather than discontinued. Management should also prioritize arrhythmia surveillance, prevention of thromboembolism (particularly with apical aneurysm or atrial fibrillation), and device therapy per standard indications with attention to scar and conduction disease.

In sum, current data support ARNI-based, guideline-directed care in heart failure due to Chagas disease, implemented with structured monitoring and system-level supports that ensure access and follow-up. Pending peer-reviewed results will refine effect sizes, durability, and subgroup guidance, but the therapeutic course for routine practice appears justified now in appropriately selected patients.

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