

MEDICAL HYPOTHESIS

The translational gap in quadruple heart failure therapy in East and Southeast Asia: Barriers and a proposed phenotype-adapted implementation model

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Abstract

Background: Quadruple guideline-directed medical therapy (GDMT) for heart failure with reduced ejection fraction (HFrEF)—composed of an angiotensin receptor-neprilysin inhibitor (ARNI) or angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEi/ARB), an evidence-based beta-blocker, a mineralocorticoid receptor antagonist (MRA), and a sodium-glucose cotransporter 2 inhibitor (SGLT2i)—produces complementary reductions in cardiovascular mortality and rehospitalization. Yet implementation across Asian health systems remains highly inconsistent. **Aim:** To synthesize contemporary implementation data from East and Southeast Asia, identify phenotype-specific and health-system barriers, and propose a testable nurse- or pharmacist-led (NPL) implementation model adapted to HFrEF populations in this subregion. **Methods:** This article integrated published HFrEF registry, health-economic, and implementation-science literature primarily from Taiwan, Singapore, the Philippines, Vietnam, China, and Japan. The synthesis was narrative and hypothesis-generating; therefore, all projected trial tables are explicitly labeled as simulated planning projections for a proposed cluster-randomized trial. **Results:** HFrEF care in East and Southeast Asia is constrained by three interacting barriers: (i) out-of-pocket medication costs and reimbursement gaps; (ii) lower body size, lower baseline systolic blood pressure, frailty, and renal-electrolyte vulnerability; and (iii) overextended outpatient infrastructure. We proposed a 3-step predischARGE-to-primary-care NPL co-management protocol that starts low-dose foundational therapy before discharge, provides algorithm-driven titration at weeks 2 and 4, and hands over stable patients to primary care by week 6. **Conclusion:** The HFrEF translational gap in East and Southeast Asia is fundamentally an implementation gap. A phenotype-adapted, protocolized NPL titration pathway deserves prospective testing as a scalable model for improving GDMT optimization across diverse health systems in the subregion. **Relevance for patients:** Safer and faster optimization of proven heart failure therapies may reduce avoidable rehospitalizations and premature mortality in vulnerable Asian HFrEF populations.

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1. Introduction

The outpatient management paradigm for heart failure with reduced ejection fraction (HFrEF) has shifted from slow sequential titration toward early, front-loaded use of four foundational drug classes.^{1,2} Contemporary quadruple therapy consists of an angiotensin receptor-neprilysin inhibitor (ARNI) or angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEi/ARB), an evidence-based beta-blocker, a mineralocorticoid receptor antagonist (MRA), and a sodium-glucose cotransporter 2 (SGLT2) inhibitor.² Each class targets distinct, complementary neurohormonal and metabolic pathways, supported by landmark clinical trials such as PARADIGM-HF³, DAPA-HF⁴, and EMPEROR-Reduced.¹ Model-based estimates suggest that comprehensive disease-modifying therapy can reduce the risk of cardiovascular death or heart-failure hospitalization by over 60% compared with older therapeutic assumptions. However, the exact magnitude varies by background therapy and patient compliance.^{5,6}

Despite clear international guideline endorsements, translating trial efficacy into everyday clinical practice remains incomplete.^{1,2} This breakdown is highly evident across East and Southeast Asian healthcare systems, where clinical phenotypes, reimbursement structures, outpatient capacity, and physician risk tolerance may differ from the Western environments in which foundational HFrEF trials were primarily conducted.^{7,8} The evidence base synthesized here is drawn primarily from Taiwan, Singapore, the Philippines, Vietnam, China, and Japan, purposively selected to represent socioeconomically and structurally diverse health systems within East and Southeast Asia; it is not intended as a comprehensive sample of all Asian health systems. This article examines this subregional HFrEF translational gap and proposes a phenotype-adapted, decentralized implementation model. The hypothesis is not that nurse- or pharmacist-led (NPL) titration is unique; that concept has been validated globally.^{9,10} Rather, our original contribution is the explicit adaptation of an NPL titration pathway to the hemodynamic, economic, workforce, and structural limits encountered in these settings.^{11,12}

2. Literature synthesis approach

We performed a targeted narrative synthesis of peer-reviewed literature on HFrEF quadruple therapy, East and Southeast Asian heart failure registries, health-economic barriers, rapid guideline-directed medical therapy (GDMT) initiation, and NPL medication optimization. PubMed/MEDLINE, Embase, and World Health Organization Western Pacific regional resources were searched for literature published from January 2018 through June 2026 using combinations of

terms including “heart failure,” “reduced ejection fraction,” “guideline-directed medical therapy,” “Asia,” “pharmacist,” “nurse-led,” and “implementation.” Priority was given to landmark randomized trials, contemporary registry or cohort studies with an East or Southeast Asian country sample, implementation initiatives, health-economic studies, and pharmacist/nurse-led systematic reviews. Eligible sources were peer-reviewed original research or clinical guidelines focused on HFrEF and published in English or with an English abstract. Because this article is hypothesis-generating rather than a formal systematic review, the search and selection process was not designed to meet PRISMA criteria, and no PRISMA flow diagram is presented. The synthesis therefore remains narrative and potentially subject to selection bias. Observed data are explicitly separated from projected trial simulations to avoid implying that the proposed model has already been empirically tested in the described cluster-randomized design.

3. Synthesis of contemporary East and Southeast Asian registry and implementation data

Real-world evidence reveals a recurring subregional pattern: while initial post-discharge drug initiation may be improving, full-dose, persistent, four-pillar optimization remains highly difficult.^{7,11}

3.1. Taiwan: GWTG-HF A.S.I.A. implementation insights

Taiwan provides an instructive example from a relatively high-resource Asian setting. The Get With The Guidelines-Heart Failure Adherence to Science, Implementation in Asia (GWTG-HF A.S.I.A.) program evaluated GDMT implementation among HFrEF patients enrolled in the Taiwan Society of Cardiology HF Registry and showed that structured quality-improvement participation was associated with higher GDMT prescription rates in participating hospitals.⁷ This supports a central premise of the present paper: evidence adoption does not occur organically. It requires system redesign, clinical champions, performance feedback, and workflow support.⁷

3.2. Vietnam and Southeast Asia: High prescription can mask low dose intensity

Several Southeast Asian reports suggest that apparent prescription rates may overestimate true therapeutic implementation when dose intensity is not audited. In the authors' clinical experience, a “prescription placeholder” pattern may occur in which all four classes appear on the discharge medication list while patients remain on introductory doses because of concerns about hypotension, renal dysfunction, frailty, affordability, or follow-up access.

This observation should be regarded as a hypothesis-generating implementation signal rather than a quantified regional fact. Accordingly, implementation metrics should include target-dose or maximum-tolerated-dose achievement rather than prescription presence alone.^{11,12}

3.3. The Philippines: Out-of-pocket expenditure and post-discharge fragility

In the Philippines, the macroeconomic barrier is particularly prominent. Philippine health-economic data estimate out-of-pocket health spending at 44.4% of current health expenditure, creating a national heart failure economic burden approaching PHP 80.9 billion.⁸ These figures support the argument that novel HFrEF agents cannot be implemented solely through physician education. Any clinically serious implementation model must address affordability, reimbursement, supply continuity, and avoidable rehospitalization costs.⁸ Locally, multicenter data show high post-discharge vulnerability, emphasizing that the lack of dedicated outpatient infrastructure directly impedes therapeutic optimization.¹¹

3.4. Singapore, China, and Japan: Broad regional gaps with different mechanisms

Singapore data show substantial gaps in GDMT prescription, dosing, and long-term persistence among eligible HFrEF patients despite a comparatively organized health system.¹² In China and Japan, available reports likewise indicate heterogeneous implementation shaped by local institutional capacity, age, multimorbidity, and treatment tolerance; these observations should not be interpreted as uniform national patterns. Collectively, the evidence indicates that the East and Southeast Asian gap is not a single phenomenon but a family of implementation gaps with different dominant mechanisms.

Workforce capacity also varies substantially across these health systems. Hospital-based clinical pharmacists are established in tertiary and secondary care in the Philippines under the Philippine Pharmacy Act (Republic Act No. 10918), and clinical pharmacy or advanced nursing roles are present to varying degrees in Taiwan, Singapore, Japan, and urban Chinese centers; community and rural capacity is less consistent, including in parts of Vietnam and the Philippines. Scope-of-practice rules for medication titration also differ and often require physician authorization or cosignature. These differences make the general practitioner or primary-care physician particularly important for maintenance and monitoring after initial titration, and they support treating the NPL pathway as an adaptable co-management framework rather than a rigid pharmacist-only model.

4. East and Southeast Asia-specific barriers to translation

The proposed East and Southeast Asian translational-gap model identifies high out-of-pocket spending, infrastructure deficits, lower average patient body mass index, and borderline baseline hemodynamics as factors that may contribute to clinician caution during uptitration (a hypothesis-level construct). This translational-gap model contrasts with the proposed 3-step NPL co-management protocol, outlining low-dose predischARGE initiation, rapid safety- and algorithm-guided titration checks at weeks 2 and 4, and structured primary-care maintenance handover by week 6. [Figure 1](#) summarizes these two components.

4.1. Macroeconomic and reimbursement barriers

While generic beta-blockers, ACEi/ARBs, and spironolactone are widely available, ARNIs and SGLT2 inhibitors remain financially out of reach for many patients in developing Asian settings. In environments with high out-of-pocket payments, clinicians may prescribe what patients can afford rather than what guidelines recommend, resulting in partial or intermittent therapy.⁸

4.2. Clinico-phenotypic variation

Published cohorts from East and Southeast Asia have documented heterogeneity in body size, systolic blood pressure, frailty, diabetes, and chronic kidney disease among patients with HF.^{12–15} In the 2026 Singapore multicentre cohort, mean systolic blood pressure at enrollment was approximately 103 mmHg, illustrating the limited hemodynamic reserve encountered in at least some regional HFrEF populations.¹² Analyses from the Asian Sudden Cardiac Death in Heart Failure registry also demonstrate a substantial burden of renal disease and frailty across participating Asian populations.^{14,15} Clinically, these features may constrain dose escalation. The further proposition that clinician risk aversion contributes to persistent under-titration is a hypothesis-level interpretation of the observed implementation gap rather than a directly measured regional behavioral trait.

4.3. Structural limits of outpatient infrastructure

In many Asian tertiary clinics, high outpatient volume leaves limited time for frequent blood pressure review, laboratory monitoring, adherence counseling, diuretic adjustment, and multidrug dose escalation.² Because the exact number of patients per clinic session varies across regional contexts, this systemic barrier is best characterized as high-volume, low-time outpatient practice, which heavily promotes clinical inertia.

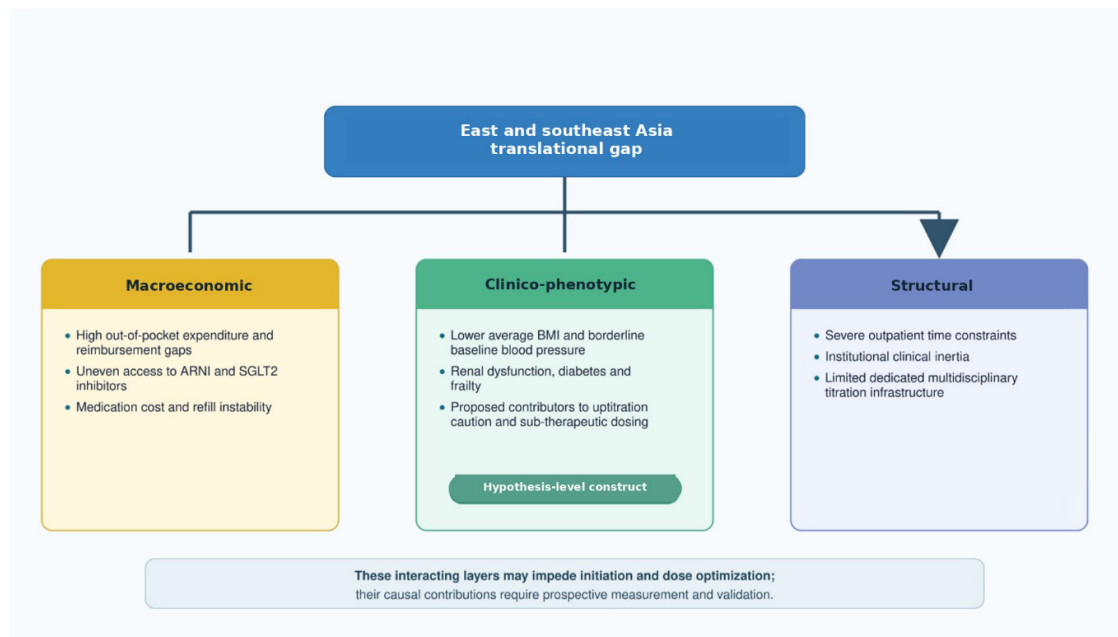


Figure 1. Hierarchical model of regional barriers to quadruple therapy execution in East and Southeast Asia
Abbreviations: ARNI: Angiotensin receptor-neprilysin inhibitor; BMI: Body mass index; SGLT2: Sodium-glucose cotransporter 2.

5. The hypothesis: A phenotype-adapted nurse- or pharmacist-led implementation framework for East and Southeast Asia

Based on the foregoing evidence synthesis and identified implementation barriers, we propose the following two interrelated hypotheses for prospective evaluation:

- Hypothesis I: The HFrEF translational gap in the East and Southeast Asian settings examined here may reflect a combined implementation failure involving limited hemodynamic reserve, laboratory-monitoring constraints, medication cost, workforce capacity, and physician-dependent workflows; clinician risk aversion is proposed as one potential contributor rather than an established empirical fact.
- Hypothesis II: A decentralized 3-step NPL co-management protocol can increase the proportion of recently hospitalized HFrEF patients reaching target or maximum tolerated doses (MTDs) of quadruple therapy within 6 weeks post-discharge without a clinically unacceptable increase in symptomatic hypotension, severe hyperkalemia, or acute kidney injury.

This model rests on an established global evidence base. Systematic reviews and meta-analyses have already linked NPL GDMT interventions to improved initiation

and dose optimization, and virtual-ward and clinic models have validated pharmacist-led rapid up-titration.^{9,10} The novelty proposed here is not the general NPL concept, but its structured application to Asian HFrEF phenotypes, reimbursement realities, and outpatient capacity constraints.

6. Proposed implementation model: The 3-step nurse- or pharmacist-led co-management protocol

The proposed co-management protocol comprises three sequential steps:

- (i) Step 1: PredischARGE low-dose initialization, inpatient phase (days -2 to 0)

For eligible patients hospitalized with acute decompensated HFrEF, initiate all four foundational classes before discharge or in rapid succession once congestion, perfusion, renal function, and potassium are clinically acceptable.¹⁶ SGLT2 inhibitors are used at their standard therapeutic dose (e.g., empagliflozin 10 mg once daily), while ARNI/ACEi/ARB, beta-blocker, and MRA therapy begin at low doses depending on blood pressure, heart rate, kidney function, potassium level, and congestion status. Initial sequencing and dose escalation are adapted to baseline blood pressure, renal function, age, and frailty according to the phenotype decision matrix (Table 1).

(ii) Step 2: NPL hemodynamic- and safety-guided titration, outpatient weeks 2 to 4

At weeks 2 and 4, the patient is reviewed in an NPL titration clinic using a preauthorized algorithm¹⁰ and the phenotype-adapted decision matrix in Table 1. The nurse or pharmacist assesses symptoms, orthostatic blood pressure, weight trajectory, congestion, heart rate, adherence, affordability, creatinine/estimated glomerular filtration rate (eGFR), potassium, and natriuretic peptide trends where available. For patients with borderline systolic blood pressure but no hypoperfusion, the algorithm prioritizes review of nonfoundational vasodilators, excessive diuresis, dehydration, and other reversible contributors before down-titrating life-saving foundational therapy. This safety-follow-up approach is consistent with rapid up-titration principles tested in the STRONG-HF trial.¹⁷ Step 2 decisions are primarily safety- and hemodynamic-driven, while biomarkers support baseline stratification and longitudinal tracking. Point-of-care renal function and electrolyte testing is preferred where available; where it is not reliably available, titration visits should be co-located with existing laboratory services. For patients

with transport barriers, selected week 2 and week 4 reviews may be conducted by telehealth, provided that a validated home blood-pressure device, reliable medication access or delivery, and timely laboratory testing are available, consistent with the virtual-ward precedent reported by Alhakem *et al.*¹⁰

These three categories are pragmatic titration strata designed to guide algorithm-based dose escalation decisions in resource-constrained outpatient settings; they do not represent discrete biological phenotypes unique to Asian populations, nor are they intended to define exhaustive or mutually exclusive clinical entities. Individual patient judgment and cardiologist review remain paramount, particularly for patients who do not fit neatly within any single category or who present with additional complexity not captured by these three strata.

(iii) Step 3: Primary care handover and maintenance, outpatient week 6 and beyond

Once target doses or MTDs are reached, the patient is handed over to a primary-care physician or general practitioner with a written maintenance plan that includes

Table 1. Phenotype-adapted titration decision matrix

Phenotype	Operational definition	Preferred sequencing	Dose increment/ interval	Safety monitoring	Mandatory cardiologist escalation triggers
A. Standard	SBP $\geq$ 100 mmHg; eGFR $\geq$ 45 mL/min/1.73 m ² ; age < 75 years; no clinically significant frailty	Concurrent/rapid initiation of all four pillars as tolerated	~25% of target dose every two weeks for titratable agents	Renal function/ electrolytes at least every two weeks during active titration	SBP < 85 mmHg; K ⁺ > 5.5 mEq/L; eGFR decline $\geq$ 25%; symptomatic hypoperfusion or decompensation
B. Low-BP	SBP 85–99 mmHg without shock or symptomatic hypoperfusion	SGLT2i first; then low-dose MRA; reduced-dose ARNI/ACEi/ARB; beta-blocker according to heart rate/congestion and stability	~12.5% of target dose every three weeks; reassess reversible causes of low BP before reducing foundational therapy	BP/orthostatic symptoms at each contact; renal function/electrolytes every 2–3 weeks or sooner after dose change	Same red flags; immediate cardiologist review for symptomatic hypotension or SBP < 85 mmHg
C. CKD/ frailty	eGFR 30–44 mL/min/1.73 m ² and/or CFS $\geq$ 4	Prioritize SGLT2i when eligible; cautious low-dose MRA and RAAS inhibition; beta-blocker individualized; avoid simultaneous aggressive escalation	~12.5% of target dose every three weeks; one major titration step at a time when clinically prudent	Weekly renal function/electrolytes for first four weeks after initiation/intensification, then individualized	K ⁺ > 5.5 mEq/L; eGFR decline $\geq$ 25%; symptomatic hypotension; dehydration; acute illness; decompensation

Notes: Phenotype priority rule: When criteria overlap, the most conservative pathway takes precedence; Phenotype C (CKD/Frailty: eGFR 30–44 mL/min/1.73 m² or CFS $\geq$ 4) supersedes Phenotypes B and A; Phenotype B (Low BP: SBP 85–99 mmHg) supersedes Phenotype A when CKD/frailty criteria are absent; thus, a patient with SBP 90 mmHg, eGFR 35 mL/min, and CFS $\geq$ 4 is classified as Phenotype C regardless of BP; if thresholds improve during titration, the supervising cardiologist may reclassify the patient upward at the week 4 reassessment.

Abbreviations: ACEi: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; ARNI: Angiotensin receptor-neprilysin inhibitor; BP: Blood pressure; CFS: Clinical Frailty Scale; CKD: Chronic kidney disease; eGFR: Estimated glomerular filtration rate; MRA: Mineralocorticoid receptor antagonist; RAAS: Renin–angiotensin–aldosterone system; SBP: Systolic blood pressure; SGLT2i: Sodium-glucose cotransporter 2 inhibitor.

achieved doses, an individualized laboratory-monitoring schedule, warning signs, affordability and refill plan, adherence strategies, and explicit re-referral triggers. At minimum, renal function and potassium should be reassessed after clinically meaningful renin–angiotensin–aldosterone system-inhibitor/MRA dose changes and thereafter at intervals determined by stability and local standards. Re-referral is triggered by worsening congestion or New York Heart Association class, symptomatic or persistent hypotension, potassium > 5.5 mEq/L, clinically significant renal decline, recurrent syncope, major arrhythmia, or intolerance to multiple foundational classes.

6.1. Implementation feasibility: Affordability, laboratory access, telehealth, and workforce

Affordability and reimbursement must be treated as implementation variables rather than background context. The protocol therefore records medication affordability and reimbursement status at each titration contact, preferentially uses evidence-based low-cost generics when clinically appropriate (including spironolactone and carvedilol), and links patients to national or institutional subsidy mechanisms. Access to newer agents such as ARNI and SGLT2 inhibitors should be addressed through local formulary and reimbursement pathways; the World Health Organization Essential Medicines framework provides a policy lever for improving access to priority medicines.¹⁸

Laboratory feasibility is assessed before enrollment into the rapid-titration pathway. Sites should have timely creatinine/eGFR and potassium testing, preferably point-of-care testing or same-day laboratory access. Where this infrastructure is unavailable, Step 2 visits should be synchronized with existing laboratory services and dose changes deferred when safety data cannot be obtained. Telehealth may substitute for selected in-person reviews only when home blood-pressure monitoring, medication access, and laboratory follow-up are dependable.¹⁰

Workforce feasibility is likewise site-specific. Where trained clinical pharmacists or advanced-practice nurses cannot safely perform algorithm-based titration within local scope-of-practice rules, a general practitioner-led or primary-care-physician-led version of the same simplified algorithm may be used with cardiologist oversight; pharmacists may then support medication reconciliation, adherence, affordability review, and quality assurance. This flexibility is central to scalability across heterogeneous health systems.

6.2. Delineation of clinical responsibilities

The safe execution of this decentralized model is structured upon clearly defined clinical boundaries and preset transition triggers.^{9,17} The care-team responsibilities and escalation criteria are summarized in [Table 2](#).

Table 2. Clinical responsibilities and escalation triggers in the NPL co-management model

Care level/role	Core clinical responsibilities	Action thresholds and escalation triggers
Supervising cardiologist	Confirms HFrEF diagnosis and eligibility; authorizes inpatient initiation and titration protocol; adjudicates complex dilemmas; reviews structural complications.	Initial diagnosis confirmation; review if cardiogenic shock, advanced valve disease, refractory congestion, recurrent syncope, or major arrhythmia occurs.
Nurse or clinical pharmacist	Runs titration algorithm; checks symptoms, BP, HR, weight, adherence, affordability, renal function, and potassium; reinforces education and telehealth follow-up; documents titration decisions. ¹⁷	Escalates dose when stable; holds or modifies titration for symptomatic hypotension, potassium > 5.5 mEq/L, marked renal decline, or clinical decompensation; contacts cardiologist for predefined red flags.
Primary-care physician/general practitioner	Maintains long-term stability; manages non-cardiac comorbidities; renews prescriptions; confirms affordability and refill continuity; monitors renal function and potassium after clinically meaningful RAAS inhibitor/MRA changes and thereafter according to stability and local standards; detects early decompensation.	Re-refers to cardiology for worsening NYHA class or congestion, symptomatic/persistent hypotension, potassium > 5.5 mEq/L, clinically significant renal decline, recurrent syncope, major arrhythmia, or intolerance to multiple foundational classes.

Abbreviations: BP: Blood pressure; GP: General practitioner; HFrEF: Heart failure with reduced ejection fraction; HR: Heart rate; MRA: Mineralocorticoid receptor antagonist; NPL: Nurse- or pharmacist-led; NYHA: New York Heart Association; RAAS: Renin–angiotensin–aldosterone system.

7. Testing the hypothesis: Proposed pragmatic evaluation

7.1. Study design and population

A future multicenter, cluster-randomized pragmatic hybrid effectiveness-implementation trial could enroll adults aged 18 years or older hospitalized for acute decompensated HFrEF with left ventricular ejection fraction $\leq 40\%$. A minimum of 12 tertiary or secondary care centers (6 per arm) across at least three participating East or Southeast Asian countries would constitute a statistical floor. Enrollment of additional centers beyond this minimum—targeting 16–20 centers where feasible—is strongly encouraged to improve the precision of between-cluster variance estimation, reduce the design effect of potential cluster-level confounders, and increase generalizability across East and Southeast Asian healthcare contexts. Stratification will be hierarchical rather than factorial: centers will first be stratified by country, and within country, assignment will aim to balance annual HF admission volume where multiple centers from the same country are enrolled. If only one center per country is available, country stratification alone will be applied without a volume sub-stratum. Centers will then be randomized 1:1 to the NPL protocol or standard institutional care using a computer-generated allocation sequence concealed at the coordinating center. Cluster-level randomization is intended to reduce contamination because titration workflows operate at the clinic level. A six-month site preparation/run-in period would establish arm-specific pathways; cross-arm contamination and crossover would be tracked through protocol-adherence audits. The simulated baseline characteristics and projected discharge process measures used for trial planning are presented in [Table 3](#).

7.2. Outcomes

The primary implementation endpoint is the proportion of patients achieving at least 75% of the guideline-recommended target dose, or a protocol-defined MTD for each of all four foundational GDMT classes within 42 days after discharge. MTD is operationally defined for this protocol as the highest dose of each GDMT class that can be maintained for ≥ 14 consecutive days without meeting any of the following stopping criteria: (i) symptomatic hypotension (systolic blood pressure < 85 mmHg with symptoms), (ii) serum potassium > 5.5 mEq/L on two consecutive measurements, (iii) eGFR decline $> 30\%$ from enrollment baseline confirmed on repeat testing within seven days, or (iv) New York Heart Association class deterioration by two or more classes requiring hospitalization. MTD is assessed independently for each

of the four drug classes; a patient may achieve 100% target dose of SGLT2 inhibitors and MRA while remaining at 50% for ARNI and beta-blocker, and this combination would qualify as MTD for the respective classes. This definition will be operationalized in the trial protocol's endpoint-adjudication manual. All potential MTD determinations contributing to the primary endpoint will be adjudicated by a central independent Clinical Events Committee using prespecified criteria; site investigators will provide the supporting clinical and laboratory documentation but will not adjudicate their own cases.

The exploratory secondary clinical endpoints are the prespecified all-cause mortality, HF-related rehospitalization within 90 days, composite death or HF rehospitalization, and treatment-limiting adverse events. The proposed trial is not independently powered for mortality or rehospitalization; these event estimates are exploratory and hypothesis-generating.

Lastly, safety endpoints are symptomatic hypotension requiring dose reduction, severe hyperkalemia ($K^+ > 6.0$ mEq/L), acute kidney injury ($\geq 25\%$ decline in eGFR from the preceding value), and complete discontinuation of a foundational drug because of adverse events.

7.3. Statistical considerations

For an individually randomized two-proportion comparison, the illustrative planning assumptions are 35% target-dose attainment in standard care and 65% in the NPL arm. The standard-care assumption is anchored to the 2026 Singapore cohort, which reported approximately one-third achieving $\geq 50\%$ target-dose optimization at six months¹², whereas the intervention assumption is modeled from the pharmacist-led virtual-ward experience of Alhakem *et al.*¹⁰, in which target-dose attainment approached two-thirds by six weeks. Neither source reproduces the exact proposed primary endpoint ($\geq 75\%$ target dose for all four GDMT classes by Day 42), population (East and Southeast Asian acute decompensated HFrEF), or follow-up period. The 35% versus 65% comparison therefore represents an illustrative planning assumption—a reasonable scenario informed by available proxy data—rather than an evidence-derived effect estimate for the exact proposed endpoint. Because the Singapore threshold was lower and assessed later, the 35% standard-care assumption may be generous; actual attainment at the more stringent and earlier endpoint may be considerably lower. The true between-arm difference may nonetheless be larger or smaller depending on local infrastructure, formulary access, and phenotype distribution, and investigators should re-examine the assumption using local registry data during site-feasibility assessment. With a two-sided alpha of 0.05 and 90% power, the unadjusted comparison

requires approximately 57 patients per arm. For cluster planning, an ICC of 0.05 is assumed and should be re-estimated during protocol development; with an average cluster size of 40, the design effect is $1 + (40-1) \times 0.05 = 2.95$. Allowing for clustering and conservative attrition, a planning target of approximately 246 patients per arm is retained, subject to final biostatistical recalculation using the definitive number and size distribution of clusters.¹⁹ The primary implementation endpoint will be analyzed by mixed-effects logistic regression with hospital site as a random effect. Given the small cluster count, the primary analysis will incorporate the Fay–Graubard bias-corrected sandwich variance estimator, which provides better Type I error control than the standard sandwich estimator when cluster numbers are small.²⁰ Prespecified sensitivity analyses will include a cluster-mean analysis using site-level endpoint proportions and a two-sample *t*-test with Welch correction, and permutation-based inference. Analyses will follow the intention-to-treat principle. Missing primary-outcome data will be handled by multiple imputation under a missing-at-random assumption, with best-case/worst-case sensitivity analyses. Site-level implementation fidelity will be assessed at weeks 2, 6, and 12 using a standardized checklist informed by the Consolidated Framework for Implementation Research (CFIR), including protocol adherence, staff training completion, algorithm compliance, and contamination/crossover indicators.²¹

Formula for the unadjusted two-proportion comparison is shown in **Equation 1**:

$$n \text{ per arm} = \frac{(Z_{\alpha/2} + Z_{\beta})^2 \cdot [p_1(1 - p_1) + p_2(1 - p_2)]}{(p_1 - p_2)^2} \quad (1)$$

7.4. Secondary implementation outcomes

In addition to the primary implementation endpoint and exploratory clinical outcomes (Tables 4 and 5), the following implementation-science outcomes will be collected prospectively at each site across both trial arms using standardized forms at weeks 2, 4, 6, and 12 post-discharge:

- (i) Affordability and medication access: Patient-reported monthly out-of-pocket medication expenditure (local-currency equivalent) at each follow-up; and cost-related non-adherence, defined as dose reduction or discontinuation primarily because of cost, by structured interview at weeks 6 and 12.
- (ii) Laboratory access and safety-monitoring fidelity: Proportion of scheduled point-of-care renal/electrolyte assessments completed within ± 3 days; site-level laboratory turnaround time; and proportion

of Step 2 visits with titration delayed ≥ 48 h because laboratory results were unavailable.

- (iii) Telehealth utilization: Proportion of Step 2 visits conducted remotely versus in person by site and country; completion rate of attempted telehealth sessions; and patient satisfaction measured on a 5-point Likert scale.
- (iv) Clinician/pharmacist workload: Mean pharmacist time per patient per Step 2 visit and number of cardiologist escalation contacts per patient during the six-week titration period.
- (v) Protocol fidelity: Site-level implementation fidelity score from a CFIR-adapted checklist at weeks 2, 6, and 12, expressed as the percentage of protocol elements fully adhered to; and the proportion requiring deviation from the phenotype-assigned algorithm, with reasons documented.
- (vi) These outcomes will be analyzed descriptively by arm and country to generate implementation-science hypotheses for future scale-up research and to inform CFIR-based site-level fidelity reporting.

Across these planning projections, target- or maximum-tolerated-dose attainment at Day 42 is approximately 65.9% with the NPL protocol versus 32.9% with standard care (projected risk ratio 2.00). Exploratory 90-day projections suggest HF-related rehospitalization of 11.0% versus 19.9% (projected risk ratio 0.55; projected absolute risk difference -8.9 percentage points) and composite death or HF rehospitalization of 13.8% versus 24.0% (projected risk ratio 0.58; projected absolute risk difference -10.2 percentage points). These are planning-scenario projections calculated from cumulative proportions, not observed results or powered efficacy claims; no time-to-event simulation was performed.

8. Discussion and translational significance

We make three deliberate structural choices to establish original context and ensure academic rigor. First, we explicitly state that non-physician-led neurohormonal optimization clinics represent an established global strategy rather than a wholly original blueprint.⁹ Second, we frame the clinical novelty around the specific translation and titration adaptations required for lower baseline hemodynamic thresholds, high regional out-of-pocket limits, outpatient logistics, and structured primary care handovers.^{8,12} Third, we transparently label all prospective trial tables as simulated planning metrics to eliminate analytical misrepresentation.

The implementation protocol incorporates the core principles of the landmark STRONG-HF trial: Early post-discharge tracking, compressed safety reassessments, and

Table 3. Simulated baseline characteristics and projected process measures for a proposed cluster-randomized trial

Characteristic	NPI co-management protocol (<i>n</i> = 246)	Standard institutional care (<i>n</i> = 246)
Simulated baseline characteristics		
Age, years, mean (SD)	67.4 (9.1)	68.1 (8.8)
Female sex, <i>n</i> (%)	64 (26.0)	69 (28.0)
Body mass index, kg/m ² , mean (SD)	22.8 (3.1)	23.1 (2.9)
Ischemic etiology, <i>n</i> (%)	138 (56.1)	141 (57.3)
LVEF, %, mean (SD)	28.4 (5.2)	27.9 (5.5)
Systolic blood pressure, mmHg, mean (SD)	98.5 (7.4)	99.1 (7.2)
Heart rate, beats/min, mean (SD)	78.2 (11.5)	79.1 (10.8)
eGFR, mL/min/1.73 m ² , mean (SD)	48.3 (11.2)	47.9 (11.8)
Serum potassium, mEq/L, mean (SD)	4.21 (0.35)	4.24 (0.38)
NT-proBNP, pg/mL, median [IQR]	3,450 [1,980–5,120]	3,510 [2,010–5,280]
Projected process measures at discharge (intervention-arm protocol requirements vs. standard care projections)		
ARNI/ACEi/ARB at discharge, <i>n</i> (%)	246 (100) (protocol requirement)	Projected 88.6% (registry-informed)
Beta-blocker at discharge, <i>n</i> (%)	246 (100) (protocol requirement)	Projected 93.9% (registry-informed)
MRA at discharge, <i>n</i> (%)	246 (100) (protocol requirement)	Projected 83.3% (registry-informed)
SGLT2 inhibitor at discharge, <i>n</i> (%)	246 (100) (protocol requirement)	Projected 74.0% (registry-informed)

Notes: The presented data are planning projections only and are not observed data; baseline values are simulated solely to illustrate a plausible trial population; intervention-arm 100% four-pillar discharge use is a protocol requirement, while standard-care discharge percentages are registry-informed projections; no inferential comparison or statistical testing should be performed on any values in this table.

Abbreviations: ACEi: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; ARNI: Angiotensin receptor-neprilysin inhibitor; eGFR: Estimated glomerular filtration rate; IQR: Interquartile range; LVEF: Left ventricular ejection fraction; MRA: Mineralocorticoid receptor antagonist; NT-proBNP: N-terminal pro-B-type natriuretic peptide; SD: Standard deviation; SGLT2: Sodium-glucose cotransporter 2.

accelerated drug intensification rather than indefinite low-dose maintenance.¹⁷ The Asian-specific clinical modifications introduce critical field safeguards: safe low-dose predischARGE initiation, structured algorithmic evaluation of borderline blood pressures (systolic blood pressure 85–99 mmHg), formal out-of-pocket affordability tracking⁸, and clear cardiologist escalation thresholds. From a renal-electrolyte protection standpoint, the model explicitly discourages premature discontinuation of necessary four-pillar combinations following minor serum shifts. Minor initial drops in eGFR following SGLT2 inhibitor initialization represent functional glomerular hemodynamic stabilization rather than structural parenchymal damage²², necessitating protocolized laboratory tracking rather than unguided cessation. The

phenotype-adapted branches in [Table 1](#) operationalize these safeguards by altering sequencing, dose increments, titration intervals, and laboratory surveillance according to blood pressure, renal function, and frailty.

The co-management model should be adapted to local workforce realities. In systems with limited clinical-pharmacist or advanced-practice-nurse capacity, a general practitioner-led titration pathway using the same simplified decision rules may be more scalable, with cardiologist escalation for predefined red flags and pharmacist participation focused on medication reconciliation, adherence, affordability, and quality oversight. The proposed 3-step pathway is therefore a functional model of distributed care, not a requirement for a single professional configuration.

Table 4. Planning projection for primary implementation endpoint

Outcome parameter	NPL protocol (n = 246)	Standard care (n = 246)	Projected RR
Achievement of $\geq 75\%$ targetdose or protocol-defined maximum tolerated dose for each of all four GDMT classes by Day 42	Approximately 162 of 246 (65.9%)	Approximately 81 of 246 (32.9%)	2.00
All four classes maintained at day 42	Approximately 221 of 246 (89.8%)	Approximately 128 of 246 (52.0%)	1.73
Three classes maintained	Approximately 18 of 246 (7.3%)	Approximately 64 of 246 (26.0%)	Not projected
Two classes maintained	Approximately 5 of 246 (2.0%)	Approximately 38 of 246 (15.4%)	Not projected
One class maintained	Approximately 2 of 246 (0.8%)	Approximately 16 of 246 (6.5%)	Not projected
ARNI/ACEi/ARB target-dose success	Approximately 148 of 246 (60.2%)	Approximately 54 of 246 (22.0%)	2.74
Beta-blocker target-dose success	Approximately 155 of 246 (63.0%)	Approximately 71 of 246 (28.9%)	2.18
MRA target-dose success	Approximately 212 of 246 (86.2%)	Approximately 142 of 246 (57.7%)	1.49
SGLT2 inhibitor therapeutic dose success	Approximately 238 of 246 (96.7%)	Approximately 174 of 246 (70.7%)	1.37

Notes: The presented data are planning projections only, not observed data; no inferential statistics should be derived from these values; effect estimates are illustrative planning-scenario projections informed by Senanayake *et al.*¹² (35% assumption) and Alhakem *et al.*¹⁰ (65% assumption). Abbreviations: ACEi: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; ARNI: Angiotensin receptor-neprilysin inhibitor; GDMT: Guideline-directed medical therapy; NPL: Nurse- or pharmacist-led; MRA: Mineralocorticoid receptor antagonist; RR: Risk ratio; SGLT2: Sodium-glucose cotransporter 2.

Table 5. Planning projection for exploratory clinical outcomes

Outcome metric	NPL protocol (n = 246)	Standard care (n = 246)	Projected RR/absolute risk difference
All-cause mortality, n (%)	Approximately 10 of 246 (4.1%)	Approximately 15 of 246 (6.1%)	0.67/–2.0 percentage points
HF-related rehospitalization, n (%)	Approximately 27 of 246 (11.0%)	Approximately 49 of 246 (19.9%)	0.55/–8.9 percentage points
Composite death or HF rehospitalization, n (%)	Approximately 34 of 246 (13.8%)	Approximately 59 of 246 (24.0%)	0.58/–10.2 percentage points
Symptomatic hypotension requiring dose reduction, n (%)	Approximately 22 of 246 (8.9%)	Approximately 14 of 246 (5.7%)	1.56/+3.2 percentage points
Severe hyperkalemia, $K^+ > 6.0$ mEq/L, n (%)	Approximately 5 of 246 (2.0%)	Approximately 3 of 246 (1.2%)	1.67/+0.8 percentage points
Acute kidney injury, $\geq 25\%$ eGFR decline, n (%)	Approximately 12 of 246 (4.9%)	Approximately 11 of 246 (4.5%)	1.09/+0.4 percentage points
Complete drug discontinuation due to adverse event, n (%)	Approximately 4 of 246 (1.6%)	Approximately 8 of 246 (3.3%)	0.48/–1.7 percentage points

Notes: The presented data are planning projections only, not observed data; risk ratios and absolute risk differences are calculated from projected 90-day cumulative proportions; no time-to-event simulation was performed; these illustrative planning scenarios are informed by proxy implementation data and must not be interpreted as observed or inferential effect estimates; the proposed trial is not powered for these clinical endpoints; if survival data are collected, actual analyses will use log-rank testing and Cox regression.

Abbreviations: eGFR: Estimated glomerular filtration rate; HF: Heart failure; NPL: Nurse- or pharmacist-led; RR: Risk ratio.

This hypothesis paper has several limitations. First, the evidence synthesis is narrative rather than systematic and may be affected by selection and publication bias. Second, the empirical evidence is concentrated in East and Southeast Asia and should not be generalized without validation to South Asian, Central Asian, or Middle Eastern health systems, where patient phenotypes, financing, workforce, and care infrastructure may differ. Third, several proposed mechanisms—particularly clinician risk aversion—remain hypothesis-level explanations rather than directly measured causal determinants. Fourth, the phenotype-adapted matrix and all trial outcome tables are proposed or simulated and require prospective validation. Finally, the planned trial is powered for the implementation endpoint, not mortality or rehospitalization; clinical-event outcomes must therefore be interpreted as exploratory unless a subsequent trial is separately powered for them.

9. Conclusion

The translational gap in quadruple HFrEF therapy across the East and Southeast Asian settings examined here is an important public-health and implementation-science challenge.^{7,8} It cannot be resolved by publishing more guidelines alone. A phenotype-adapted 3-step NPL co-management model offers a plausible, testable, and potentially scalable pathway to move HFrEF care from prescription presence to true therapeutic optimization.^{11,12} The next step is a pragmatic, adequately powered, cluster-randomized evaluation with explicit safety monitoring, affordability metrics, workforce and laboratory feasibility measures, implementation-fidelity assessment, and long-term persistence outcomes.

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Conflict of interest

The authors declare no competing interests.

Author contributions

Conceptualization: All authors

Methodology: Rafael R. Castillo

Writing—original draft: All authors

Writing—review and editing: All authors

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

No new patient-level dataset was generated for this medical hypothesis article. The trial tables are simulated planning projections based on registry and implementation-science literature; any future prospective trial would require ethics approval, trial registry registration, and prespecified statistical analysis.

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