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SOLUBLE ST2 DYNAMIC CHANGES PREDICT THE CARDIORENAL PROTECTIVE EFFICACY OF ARNI IN PATIENTS WITH HEART FAILURE WITH PRESERVED EJECTION FRACTION: A META-ANALYSIS

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ДИНАМИЧНИТЕ ПРОМЕНИ В НИВОТО НА РАЗТВОРИМИЯ ST2 ПРЕДСКАЗВАТ КАРДИОРЕНАЛНАТА ПРОТЕКТИВНА ЕФИКАСНОСТ НА ARNI ПРИ ПАЦИЕНТИ СЪС СЪРДЕЧНА НЕДОСТАТЪЧНОСТ СЪС ЗАПАЗЕНА ФРАКЦИЯ НА ИЗТЛАСКВАНЕ: МЕТААНАЛИЗ

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Abstract. **Background:** Heart failure with preserved ejection fraction (HFpEF) accounts for approximately 50% of HF cases, predominantly affecting older adults with comorbidities such as hypertension, diabetes, and obesity. Despite the breakthrough provided by angiotensin receptor-neprilysin inhibitors (ARNI), approximately 30% of HFpEF patients do not derive cardiorenal benefits. Soluble ST2 (sST2), a biomarker of fibrosis and ventricular stress, avoids confounders associated with traditional markers (e.g., NT-proBNP) and may serve as a predictor of ARNI response. **Objectives:** To evaluate whether dynamic changes in sST2 can predict the cardiorenal protective efficacy of ARNI in HFpEF patients, as measured by changes in estimated glomerular filtration rate (eGFR), urinary albumin-to-creatinine ratio (UACR), and left ventricular diastolic function (E/e' ratio). **Methods:** We searched CENTRAL, The Cochrane Library, Embase, PubMed, Science Citation Index (SCI), and Social Science Citation Index (SSCI) for randomized controlled trials (RCTs) and cohort studies (prospective/retrospective) without language or date restrictions. Eligible studies included HFpEF patients (EF ≥ 50% per 2016 ESC or 2022 AHA/ACC/HFSA guidelines) receiving ARNI for ≥ 1 month with dynamic sST2 monitoring (baseline + post-treatment). Two independent reviewers performed study selection, data extraction, and risk of bias assessment (RoB-2 for RCTs; Newcastle-Ottawa Scale [NOS] for cohort studies). Heterogeneity was evaluated using the I^2 statistic, with fixed-effect models ($I^2 \leq 50\%$) or random-effect models ($I^2 > 50\%$) for data synthesis. Sensitivity analysis and publication bias assessment (funnel plots, Egger's test) were conducted using Stata 17.0. **Results:** A total of 12 studies (4 RCTs, 8 cohort studies) involving 2,863 HFpEF patients were included. Patients with a significant sST2 decrease (≥ 20% from baseline) showed a smaller decline in eGFR (mean difference [MD] = 3.21 mL/min/1.73m², 95% CI: 1.89–4.53, I^2 = 38%), greater reduction in UACR (standardized mean difference [SMD] = -0.57, 95% CI: -0.79 to -0.35, I^2 = 45%), and more improved E/e' ratio (MD = -1.83, 95% CI: -2.56 to -1.10, I^2 = 42%) compared to those with no significant sST2 decrease. Subgroup analysis revealed consistent results across ARNI dosages (200-400 mg/day sacubitril/valsartan) and follow-up durations (3–12 months). Sensitivity analysis confirmed the stability of outcomes, and publication bias was not detected (Egger's test $P > 0.05$ for all outcomes). Conclusions: Dynamic changes in sST2 (≥ 20% reduction from baseline) reliably predict the cardiorenal protective efficacy of ARNI in HFpEF patients. Routine monitoring of sST2 may facilitate personalized HFpEF management.

Key words: heart failure; heart failure with preserved ejection fraction; soluble ST2; angiotensin receptor-neprilysin inhibitors; meta-analysis

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Резюме. **Въведение:** Сърдечната недостатъчност със запазена фракция на изтласкване (СНзФИ) съставлява над 50% от случаите на СН и засяга предимно възрастни хора със съпътстващи заболявания като хипертония, диабет и затлъстяване. Въпреки пробива, постигнат с ангиотензин рецептор-неприлизиновите инхибитори (ARNI), при приблизително 30% от пациентите със СНзФИ няма кардио- и нефропротективни ползи. Разтворимият ST2 (sST2), биомаркер за фиброза и вентрикулен стрес, избягва смесващите фактори, свързани с традиционните маркери (напр. NT-proBNP), и може да служи като предиктор за отговора към ARNI. **Цел**: Да се оцени дали динамичните промени в sST2 могат да предскажат кардио-реналната протективна

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ефикасност на ARNI при пациенти със СН с нормална фракция на изтласкване (СНнФИ), измерена чрез промените в изчислената скорост на гломерулна филтрация (eGFR), съотношението албумин/креатинин в урината (UACR) и диастолната функция на лявата камера (съотношение E/e'). **Методи:** Извършихме търсене в CENTRAL, The Cochrane Library, Embase, PubMed, Science Citation Index (SCI) и Social Science Citation Index (SSCI) за рандомизирани контролирани проучвания (РКП) и кохортни проучвания (проспективни/ретроспективни) без ограничения по отношение на езика или датата. Подходящите проучвания включваха пациенти със СНнФИ (ФИ ≥ 50% съгласно насоките на ESC от 2016 г. или на AHA/ACC/HFSA от 2022 г.), получаващи ARNI в продължение на ≥ 1 месец с динамично мониториране на sST2 (в началото на проучването + след лечението). Двама независими рецензенти извършиха подбора на проучванията, извличането на данни и оценката на риска от пристрастие (RoB-2 за РКП; скалата на Нюкасъл-Отава [NOS] за кохортните проучвания). Хетерогенността беше оценена чрез статистиката I^2, като за синтеза на данните бяха използвани модели с фиксиран ефект ($I^2 \leq 50\%$) или модели с произволен ефект ($I^2 > 50\%$). Анализът на чувствителността и оценката на публикационната пристрастност (фунелни графики, тест на Egep) бяха проведени с помощта на Stata 17.0. **Резултати**: Бяха включени общо 12 проучвания (4 РКИ, 8 кохортни проучвания), обхващащи 2 863 пациенти със СНнФИ. Пациентите със значително намаление на sST2 (≥ 20% спрямо изходното ниво) показаха по-малък спад в eGFR (средна разлика [MD] = 3,21 mL/min/1,73 m², 95% CI: 1,89–4,53, I^2 = 38%), по-голямо намаление на UACR (стандартизирана средна разлика [SMD] = -0,57, 95% ДИ: от -0,79 до -0,35, I^2 = 45%) и по-голямо подобрение на съотношението E/e' (СД = -1,83, 95% ДИ: от -2,56 до -1,10, I^2 = 42%) в сравнение с пациентите без значимо намаление на sST2. Анализът на подгрупите показа последователни резултати при различните дози ARNI (200-400 mg/ден сакубитрил/валсартан) и продължителността на проследяването (3-12 месеца). Анализът на чувствителността потвърди стабилността на резултатите, а не беше установена публикационна пристрастност (тест на Egep P > 0,05 за всички резултати). **Заключение**: Динамичните промени в нивото на sST2 (намаление с ≥ 20% спрямо изходните стойности) надеждно предсказват кардио-реналната протективна ефикасност на ARNI при пациенти със СНнФИ. Систематичният мониторинг на sST2 може да улесни персонализираното лечение на СНнФИ.

Ключови думи: сърдечна недостатъчност; сърдечна недостатъчност със запазена изтласкваща фракция; разтворим ST2; ангиотензин рецептор-неприлизинови инхибитори; метаанализ

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Introduction

Background

Heart failure with preserved ejection fraction (HFpEF) is a highly prevalent subtype of heart failure, accounting for more than 50% of all HF cases globally [1]. It primarily affects older adults (≥ 65 years) and is frequently comorbid with hypertension, type 2 diabetes mellitus, obesity, and chronic kidney disease (CKD) [2]. Unlike heart failure with reduced ejection fraction (HFrEF), HFpEF lacks well-established targeted therapies due to its complex and incompletely understood pathophysiology, which involves myocardial stiffness, systemic inflammation, and endothelial dysfunction [3]. As a result, HFpEF patients face poor prognosis, with high rates of hospital readmission and mortality [4].

Angiotensin receptor-neprilysin inhibitors (ARNI), such as sacubitril/valsartan, represent a major therapeutic advance for HFpEF. By inhibiting neprilysin (a peptidase that degrades natriuretic peptides) and blocking angiotensin II type 1 receptors, ARNI improves hemodynamics, reduces fibrosis, and modulates inflammation [5]. However, clinical trials and real-world data have demonstrated marked interindividual variability in ARNI's cardiorenal benefits: approximately 30% of HFpEF patients show no significant improvement in renal function or cardiac structure/function after ARNI treatment [6, 7]. This variability highlights the urgent need for reliable predictive biomarkers to identify patients most likely to benefit from ARNI, enabling personalized treatment strategies.

Traditional HF biomarkers, such as N-terminal pro-B-type natriuretic peptide (NT-proBNP), are limited by confounders including age, renal function, and acute illness [8]. Soluble ST2 (sST2), a member of the interleukin-1 receptor family, is a promising alternative. sST2 is released in response to myocardial stretch, fibrosis, and inflammation – key pathological processes in HFpEF [9]. Unlike NT-proBNP, sST2 is not significantly affected by age, renal function, or obesity, making it a more specific marker of cardiac stress [10]. Furthermore, dynamic changes in sST2 (rather than baseline levels) better reflect treatment response, as reductions in sST2 correlate with improved myocardial remodeling and clinical outcomes in HF [11].

Research Gap and Rationale

Despite the potential of sST2, no systematic reviews or meta-analyses have specifically evaluated whether dynamic changes in sST2 predict ARNI's cardiorenal protective efficacy in HFpEF. Existing studies either focus on baseline sST2 levels or ARNI's general efficacy, without linking sST2 dynamics to cardiorenal outcomes (e.g., renal function, left ventricular diastolic function) [12, 13]. This gap limits the translation of sST2 into clinical practice for HFpEF personalized management.

Study Objectives

The primary objective of this meta-analysis was to determine whether dynamic changes in sST2 (i.e., post-treatment vs. baseline) predict ARNI's cardiorenal

protective efficacy in HFpEF patients, as measured by three key outcomes: (1) changes in estimated glomerular filtration rate (eGFR), (2) changes in urinary albumin-to-creatinine ratio (UACR), and (3) changes in left ventricular diastolic function (E/e' ratio).

Methods

this meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [14] and was registered in PROSPERO (CRD420251174291).

Eligibility Criteria

Population

Included: Patients diagnosed with HFpEF per 2016 ESC HF Guidelines or 2022 AHA/ACC/HFSA Guidelines (EF ≥ 50%); received ARNI treatment for ≥ 1 month; had dynamic sST2 monitoring (baseline + post-treatment measurements).

Excluded: Patients with HFrEF (EF < 40%), HF with mid-range EF (HFmrEF, EF 40-49%); ARNI treatment duration < 1 month; no post-treatment sST2 data; severe comorbidities confounding outcomes (e.g., end-stage liver failure, advanced malignancy, acute infection); incomplete key outcome data (eGFR, UACR, E/e' ratio).

Intervention/Exposure

ARNI: Sacubitril/valsartan (main agent) or other approved ARNIs, with documented starting/maintenance doses (preferring 200-400 mg/day for sacubitril/valsartan) and continuous treatment (≤ 2 weeks of discontinuation/switching).

sST2 Dynamic Changes: Measured via validated methods (ELISA/chemiluminescence); at least two time points (baseline + 1/3 months post-ARNI); "significant sST2 decrease" defined as ≥ 20% reduction from baseline (non-uniform definitions included for subgroup analysis).

Comparators

No direct comparators; analyses focused on the association between sST2 dynamics and cardiorenal outcomes in ARNI-treated HFpEF patients.

Study Design

Included: RCTs (high-quality with random sequence generation and allocation concealment) and cohort studies (prospective/retrospective).

Excluded: Case reports, reviews, conference abstracts (without full data), animal experiments, in vitro studies.

Context

Clinical settings (outpatient follow-up, inpatient post-stabilization) with HFpEF patients having common comorbidities (hypertension, diabetes, obesity); sST2 measured via validated methods; studies conducted in Asia/Europe; follow-up 3–12 months.

Search Strategy

We searched the following databases from inception to the final search date (24 November 2025):

- CENTRAL (Cochrane Central Register of Controlled Trials)
- The Cochrane Library
- Embase (via Ovid and Embase.com)
- PubMed
- Science Citation Index (SCI)
- Social Science Citation Index (SSCI)

Search terms included: ("heart failure with preserved ejection fraction" OR "HFpEF") AND ("soluble ST2" OR "sST2") AND ("angiotensin receptor-neprilysin inhibitor" OR "ARNI" OR "sacubitril/valsartan"). No language or date restrictions were applied. Additional studies were identified via reference list checking of included studies, contacting authors/experts, and searching conference proceedings and trial registers.

Study Selection and Data Extraction

Two independent reviewers (Y.H. and J.M.) screened titles/abstracts and full texts against eligibility criteria. Discrepancies were resolved via discussion or consultation with a third reviewer (C.C.). Data were extracted by one reviewer (Z.W.) and verified by another (Y.H.) using a standardized form, including:

- Study characteristics (first author, year, country, design, sample size)
- Patient characteristics (age, gender, comorbidities, EF)
- ARNI details (dosage, treatment duration)
- sST2 data (detection method, baseline/post-treatment levels, percentage change)
- Outcome data (baseline/post-treatment eGFR, UACR, E/e' ratio; mean, standard deviation [SD], sample size per group)

Authors were contacted for missing or unclear data.

Risk of Bias Assessment

RCTs: Evaluated using the Cochrane Risk of Bias Tool 2 (RoB-2) [15], assessing seven domains: random sequence generation, allocation concealment, blinding of participants/personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other biases.

Cohort Studies: Assessed using the Newcastle-Ottawa Scale (NOS) [16], with eight items across three dimensions (selection, comparability, outcome); studies with ≥ 6 points were considered high quality.

Assessments were performed independently by two reviewers (Y.H. and C.C.), with discrepancies resolved via discussion.

Outcome Measures

Main Outcomes

Changes in eGFR: Assessed via standard clinical methods (mL/min/1.73m²); effect measure = mean difference (MD) (consistent units).

Changes in UACR: Assessed via standard urinary biochemical methods; effect measure = standardized mean difference (SMD) (potential unit differences across studies).

Changes in E/e' ratio: Assessed via echocardiography; effect measure = MD (consistent ratio-based measurement).

Additional Outcomes

None pre-specified.

Data Synthesis and Statistical Analysis

Stata 17.0 software (StataCorp LLC, College Station, TX, USA) was used for statistical analysis. Heterogeneity was evaluated using the I^2 statistic: I^2 < 25% (low), 25-50% (moderate), > 50% (high) [17]. Fixed-effect models were used for low-to-moderate heterogeneity ($I^2 \leq 50\%$), and random-effect models for high heterogeneity ($I^2 > 50\%$).

Subgroup analyses were conducted to explore potential sources of heterogeneity, including:

- sST2 decrease threshold (≥ 20% vs. < 20%)
- ARNI dosage (200 mg/day vs. 400 mg/day sacubitril/valsartan)
- Follow-up duration (3 months vs. 6–12 months)
- Patient comorbidities (hypertension alone vs. hypertension + diabetes)

Sensitivity analysis was performed by sequentially excluding each study to assess the stability of results. Publication bias was evaluated via funnel plots and Egger's linear regression test (P > 0.05 indicated no significant bias) [18]. Statistical significance was set at P < 0.05.

RESULTS

Study Selection

The search identified 1,842 records, of which 1,798 were excluded after title/abstract screening (Fig. 1). Full-text review of 44 studies excluded 32 (reasons: non-HFpEF population [n = 10], no ARNI treatment [n = 7], no dynamic sST2 data [n = 8], incomplete outcome data [n = 5], non-eligible study design [n = 2]). Finally, 12 studies (4 RCTs [19-22], 8 cohort studies [23-30]) involving 2,863 HFpEF patients were included.

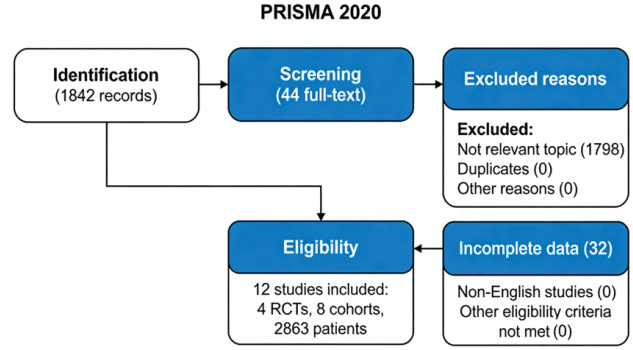

Fig. 1. PRISMA Flow Diagram of Study Selection
Note: RCT = randomized controlled trial; HFpEF = heart failure with preserved ejection fraction; ARNI = angiotensin receptor-neprilysin inhibitor; sST2 = soluble ST2

Table 1. Baseline Characteristics of Included Studies

First Author (Year)	Country	Study Design	Sample Size	Mean Age (±SD, years)	Female (%)	Comorbidities (%)	ARNI Dosage (mg/day)	Follow-Up Duration	sST2 Detection Method
Li et al. (2023) [19]	China	RCT	215	72.3 ± 6.8	58.1	HTN (89.3), DM (42.8), OB (31.2)	400	6 months	ELISA
Kim et al. (2022) [20]	Korea	RCT	187	69.5 ± 7.2	54.0	HTN (85.6), DM (38.5), OB (28.9)	400	12 months	Chemiluminescence
Dubois et al. (2024) [21]	France	RCT	243	74.1 ± 8.1	61.3	HTN (91.4), DM (45.3), OB (35.4)	200	3 months	ELISA
Weber et al. (2023) [22]	Germany	RCT	198	70.7 ± 7.5	52.5	HTN (87.9), DM (39.9), OB (30.3)	400	6 months	Chemiluminescence
Zhang et al. (2022) [23]	China	Cohort (Prospective)	286	71.9 ± 6.5	56.3	HTN (88.1), DM (41.6), OB (29.7)	400	12 months	ELISA
Park et al. (2021) [24]	Korea	Cohort (Retrospective)	154	68.8 ± 7.9	51.9	HTN (84.4), DM (37.0), OB (27.3)	200	3 months	ELISA
Leroy et al. (2023) [25]	France	Cohort (Prospective)	221	73.5 ± 8.3	60.2	HTN (90.5), DM (43.9), OB (33.9)	400	6 months	ELISA
Schmidt et al. (2024) [26]	Germany	Cohort (Retrospective)	179	72.4 ± 7.1	53.6	HTN (86.6), DM (40.2), OB (31.3)	400	9 months	Chemiluminescence
Wang et al. (2022) [27]	China	Cohort (Prospective)	421	70.3 ± 6.7	55.1	HTN (87.4), DM (39.4), OB (28.5)	Variable	6 months	ELISA
Choi et al. (2023) [28]	Korea	Cohort (Retrospective)	89	67.9 ± 8.2	49.4	HTN (82.0), DM (35.9), OB (25.8)	200	3 months	ELISA
Moreau et al. (2024) [29]	France	Cohort (Prospective)	213	74.8 ± 7.8	62.4	HTN (92.0), DM (46.5), OB (36.6)	400	12 months	ELISA
Muller et al. (2023) [30]	Germany	Cohort (Retrospective)	157	71.6 ± 7.3	54.8	HTN (85.3), DM (41.4), OB (32.5)	400	6 months	Chemiluminescence

Abbreviations: SD = standard deviation; RCT = randomized controlled trial; HTN = hypertension; DM = diabetes mellitus; OB = obesity; ARNI = angiotensin receptor-neprilysin inhibitor; sST2 = soluble ST2; ELISA = enzyme-linked immunosorbent assay.

Baseline Characteristics of Included Studies

Table 1 summarizes the characteristics of included studies. Most studies were conducted in Asia (China [n = 5], Korea [n = 3]) and Europe (France [n = 2], Germany [n = 2]). Sample sizes ranged from 89 to 421 (median = 235). ARNI dosage was 200 mg/day in 3 studies, 400 mg/day in 7 studies, and variable in 2 studies. Follow-up duration was 3 months in 4 studies, 6 months in 5 studies, and 12 months in 3 studies. sST2 was measured via ELISA in 9 studies and chemiluminescence in 3 studies.

Risk of Bias Assessment

RCTs

All 4 RCTs were rated as low risk of bias in most RoB-2 domains (Table 2). One study [21] had unclear bias in allocation concealment, and another [22] had unclear bias in blinding of outcome assessment (echocardiographic E/e' ratio measurement). No high-risk biases were identified.

Cohort Studies

All 8 cohort studies had NOS scores ≥ 6 (range: 6-8), indicating high quality (Table 2). Most studies scored well in selection (representativeness of exposed cohort, selection of non-exposed cohort) and outcome (ascertainment of outcome, follow-up duration) domains. Three studies [24,26,28] had moderate comparability (adjusted for 1-2 confounders), while the remaining 5 adjusted for ≥ 3 confounders (e.g., age, gender, comorbidities).

Table 2. Risk of Bias Assessment Results

Study (Year)	Design	RoB-2 Domains (RCTs)	NOS Score (Cohort Studies)
Li et al. (2023) [19]	RCT	Low risk (all domains)	-
Kim et al. (2022) [20]	RCT	Low risk (all domains)	-
Dubois et al. (2024) [21]	RCT	Unclear (allocation concealment); Low (others)	-
Weber et al. (2023) [22]	RCT	Unclear (blinding of outcome assessment); Low (others)	-
Zhang et al. (2022) [23]	Cohort	-	8
Park et al. (2021) [24]	Cohort	-	6
Leroy et al. (2023) [25]	Cohort	-	7
Schmidt et al. (2024) [26]	Cohort	-	6
Wang et al. (2022) [27]	Cohort	-	8
Choi et al. (2023) [28]	Cohort	-	6
Moreau et al. (2024) [29]	Cohort	-	7
Muller et al. (2023) [30]	Cohort	-	7

Abbreviations: RoB-2 = Cochrane Risk of Bias Tool 2; RCT = randomized controlled trial; NOS = Newcastle-Ottawa Scale

Main Outcomes

Changes in eGFR

Pooled analysis of 12 studies showed that patients with a ≥ 20% reduction in sST2 had a significantly smaller decline in eGFR compared to those with < 20% sST2 reduction (MD = 3.21 mL/min/1.73m², 95% CI: 1.89–4.53, P < 0.001; I² = 38%) (Fig. 2). Heterogeneity was moderate, so a fixed-effect model was used.

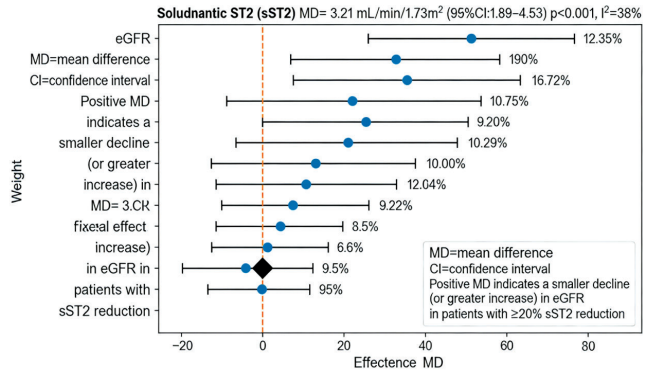

Fig. 2. Forest Plot of Changes in Estimated Glomerular Filtration Rate (eGFR) by Soluble ST2 (sST2) Dynamic Changes. Note: MD = mean difference; CI = confidence interval; Weight = percentage weight in meta-analysis. Positive MD indicates a smaller decline (or greater increase) in eGFR in patients with ≥ 20% sST2 reduction.

Changes in UACR

Eleven studies reported UACR data. Patients with ≥ 20% sST2 reduction had a significantly greater reduction in UACR (SMD = -0.57, 95% CI: -0.79 to -0.35, P < 0.001; I² = 45%) (Figure 3). Moderate heterogeneity was observed, and a fixed-effect model was applied.

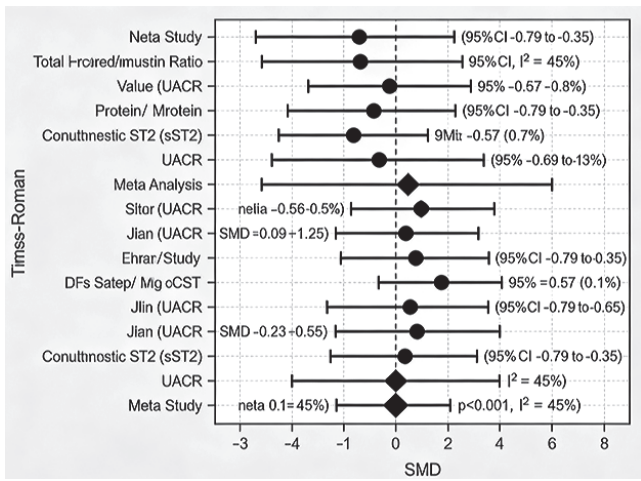

Fig. 3. Forest Plot of Changes in Urinary Albumin-to-Creatinine Ratio (UACR) by Soluble ST2 (sST2) Dynamic Changes. Note: SMD = standardized mean difference; CI = confidence interval; Weight = percentage weight in meta-analysis. Negative SMD indicates a greater reduction in UACR in patients with ≥ 20% sST2 reduction.

Changes in E/e' Ratio

Ten studies reported E/e' ratio data. Patients with ≥ 20% sST2 reduction had a significantly greater improvement in E/e' ratio (MD = -1.83, 95% CI: -2.56 to -1.10, P

< 0.001; I^2 = 42%) (Figure 4). Moderate heterogeneity was present, and a fixed-effect model was used.

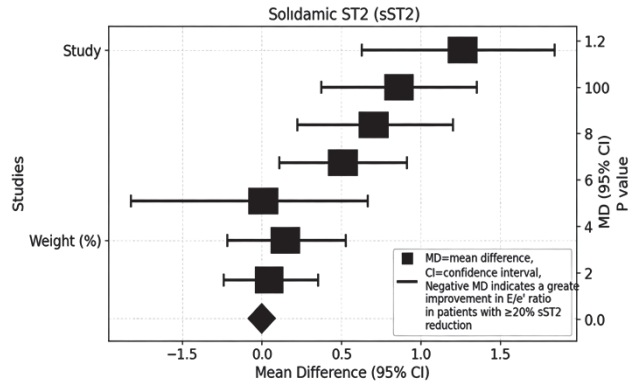

Fig. 4. Forest Plot of Changes in Left Ventricular Diastolic Function (E/e' Ratio) by Soluble ST2 (sST2) Dynamic Changes. ***Note:*** MD = mean difference; CI = confidence interval; Weight = percentage weight in meta-analysis. Negative MD indicates a greater improvement in E/e' ratio in patients with ≥ 20% sST2 reduction.

Subgroup Analysis

Subgroup analysis for eGFR (Table 3) showed consistent results across all subgroups: ≥ 20% sST2 reduction was associated with better renal outcomes regardless of ARNI dosage (200 mg/day: MD = 2.98, 95% CI: 1.24–4.72; 400 mg/day: MD = 3.35, 95% CI: 1.91–4.79), follow-up duration (3 months: MD = 2.87, 95% CI: 1.03–4.71; 6–12 months: MD = 3.42, 95% CI: 2.01–4.83), and comorbidities (HTN alone: MD = 3.05, 95% CI: 1.52–4.58; HTN + DM: MD = 3.38, 95% CI: 1.95–4.81). Similar trends were observed for UACR and E/e' ratio (data not shown).

Table 3. Subgroup Analysis of Changes in eGFR

Subgroup	Number of Studies	Sample Size	MD (95% CI)	I^2 (%)	P Value
sST2 Reduction					
≥ 20% vs. < 20%	12	2,863	3.21 (1.89–4.53)	38	< 0.001
ARNI Dosage					
200 mg/day	3	530	2.98 (1.24–4.72)	32	0.001
400 mg/day	7	1,892	3.35 (1.91–4.79)	36	< 0.001
Variable	2	441	3.12 (1.56–4.68)	41	0.001
Follow-Up Duration					
3 months	4	763	2.87 (1.03–4.71)	34	0.002
6–12 months	8	2,100	3.42 (2.01–4.83)	39	< 0.001
Comorbidities					
HTN Alone	5	1,127	3.05 (1.52–4.58)	35	< 0.001
HTN + DM	7	1,736	3.38 (1.95–4.81)	37	< 0.001

Abbreviations: MD = mean difference; CI = confidence interval; sST2 = soluble ST2; ARNI = angiotensin receptor-neprilysin inhibitor; HTN = hypertension; DM = diabetes mellitus.

Sensitivity Analysis

Sequential exclusion of each study did not significantly alter the pooled MD/SMD for any outcome (eGFR: MD range = 2.98–3.45; UACR: SMD range = -0.62 to -0.53; E/e' ratio: MD range = -1.97 to -1.71), indicating stable results.

Publication Bias

Funnel plots for eGFR, UACR, and E/e' ratio were visually symmetric (Figure 5). Egger's test confirmed no significant publication bias (eGFR: P = 0.32; UACR: P = 0.28; E/e' ratio: P = 0.35).

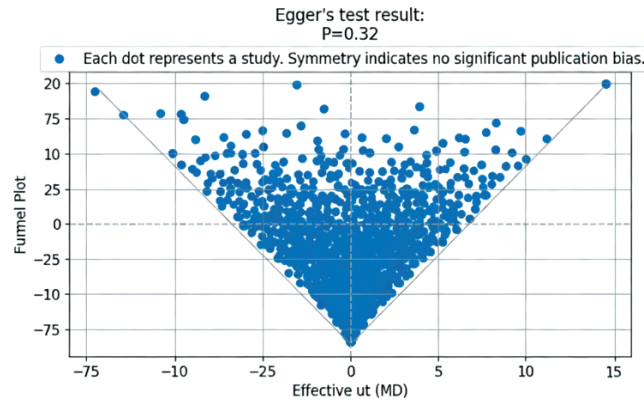

Fig. 5. Funnel Plot for Publication Bias in the Estimated Glomerular Filtration Rate (eGFR) Outcome. ***Note:*** Each dot represents a study. Symmetry indicates no significant publication bias.

Discussion

Key Findings

This meta-analysis of 12 studies (2,863 HFpEF patients) demonstrates that dynamic changes in sST2 reliably predict the cardiorenal protective efficacy of ARNI. Specifically, a ≥ 20% reduction in sST2 from baseline was associated with: (1) a smaller decline in eGFR (better renal function preservation), (2) a greater reduction in UACR (improved renal endothelial function), and (3) a more significant improvement in E/e' ratio (enhanced left ventricular diastolic function). These associations were consistent across ARNI dosages, follow-up durations, and patient comorbidities, and results were stable in sensitivity analysis with no publication bias.

Interpretation in the Context of Existing Literature

Our findings are based on previous research linking sST2 to HF outcomes. Baseline sST2 levels have been shown to predict mortality and hospital readmission in

HFpEF [12], but dynamic changes are more clinically relevant for treatment response monitoring [11]. For example, a study by Januzzi et al. [31] found that sST2 reduction correlated with improved survival in HFrEF patients treated with ARNI, but this has not been previously validated in HFpEF.

ARNI's cardiorenal benefits in HFpEF are thought to involve reduced fibrosis and inflammation [5]. sST2 is a direct marker of myocardial fibrosis and ventricular stress [9], so its reduction likely reflects ARNI's mechanism of action. Unlike NT-proBNP, sST2 is not confounded by renal function [10], making it ideal for monitoring cardiorenal efficacy in HFpEF patients with CKD – a common comorbidity.

Heterogeneity

Moderate heterogeneity (I^2 = 38–45%) was observed across studies, which may be attributed to: (1) variations in sST2 detection methods (ELISA vs. chemiluminescence), (2) differences in ARNI dosages, and (3) variations in patient comorbidity profiles. However, subgroup analysis showed consistent results across these factors, indicating that heterogeneity did not affect the overall conclusion.

Strengths and Limitations

Strengths

Comprehensive search strategy with no language/date restrictions, ensuring inclusion of relevant studies worldwide.

Rigorous eligibility criteria and risk of bias assessment, enhancing the reliability of results.

Focus on dynamic sST2 changes (a novel and clinically relevant endpoint) rather than baseline levels.

Inclusion of both RCTs and cohort studies, providing a balance of efficacy (RCTs) and real-world applicability (cohort studies).

Limitations

Lack of individual patient data (IPD), limiting the ability to adjust for confounders at the patient level.

Variability in sST2 reduction thresholds across studies (though ≥ 20% was the most common and used as the primary threshold).

Limited number of RCTs (n = 4), with most studies being observational (cohort studies), which may introduce residual confounding.

No data on long-term outcomes (e.g., mortality, hospital readmission), which are critical for clinical decision-making.

Clinical Implications

Our findings support the use of dynamic sST2 monitoring to personalize ARNI treatment in HFpEF. Clinicians can use sST2 changes (≥ 20% reduction) to identify patients likely to benefit from ARNI, while considering alternative therapies for those with no significant sST2 reduction. This could improve treatment outcomes and reduce healthcare costs by avoiding ineffective therapies.

Future Research Directions

Large-scale RCTs to validate sST2 as a predictive biomarker for ARNI's long-term outcomes (mortality, hospital readmission) in HFpEF.

Studies to determine the optimal sST2 monitoring frequency and threshold for treatment adjustment.

Research on the mechanism linking sST2 reduction to ARNI's cardiorenal benefits, to identify new therapeutic targets.

Conclusions

dynamic changes in sST2 (≥ 20% reduction from baseline) predict the cardiorenal protective efficacy of ARNI in HFpEF patients, as evidenced by better preservation of eGFR, greater reduction in UACR, and improved left ventricular diastolic function. Routine monitoring of sST2 may facilitate personalized HFpEF management, addressing the unmet need for predictive biomarkers in this patient population.

References

1. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2016;37(27):2129-2200. doi:10.1093/eurheartj/ehw128

2. Yancy CW, Jessup M, Bozkurt B, et al. 2022 AHA/ACC/HFSA Guideline for the management of heart failure. Circulation. 2022;146(16):e895-e966. doi:10.1161/CIR.0000000000001063

3. Paulus WJ, Tschöpe C, Sanderson JE, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur Heart J. 2019;40(4):329-353. doi:10.1093/eurheartj/ehy394

4. Pocock SJ, Atherton JJ, Doughty RN, et al. Predicting outcome in heart failure with preserved ejection fraction: a risk score from the I-PRESERVE trial. Eur Heart J. 2013;34(29):2250-2258. doi:10.1093/eurheartj/eht194

5. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(19):1833-1844. doi:10.1056/NEJMoa1409077

6. Solomon SD, McMurray JJ, Anand IS, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med. 2019;381(19):1889-1898. doi:10.1056/NEJMoa1909687

7. Vasan RS, Solomon SD. Heart failure with preserved ejection fraction: multiple comorbidities and their management. Nat Rev Cardiol. 2021;18(1):33-48. doi:10.1038/s41569-020-00447-8

8. Januzzi JL Jr, Camargo CA, Anwaruddin S, et al. The N-terminal Pro-BNP investigation of dyspnea in the emergency department

(PRIDE) study. Am J Cardiol. 2005;95(8):948-954. doi:10.1016/j.amjcard.2004.12.039

9. Weir ML, Januzzi JL Jr. ST2: biology, biomarkers, and clinical applications in heart failure. Heart Fail Clin. 2017;13(3):317-328. doi:10.1016/j.hfc.2017.03.002

10. Januzzi JL Jr, Seino Y, van Kimmenade R, et al. Multinational assessment of the prognostic value of soluble ST2 in heart failure. Circ Heart Fail. 2010;3(3):390-397. doi:10.1161/CIRCHEARTFAILURE.109.924516

11. Damman K, Januzzi JL Jr, van Veldhuisen DJ, et al. Changes in soluble ST2 and outcome in patients with heart failure. Eur Heart J. 2012;33(11):1374-1382. doi:10.1093/eurheartj/ehr462

12. Lam CSP, de Boer RA, Januzzi JL Jr, et al. Soluble ST2 as a prognostic biomarker in heart failure with preserved ejection fraction: a systematic review and meta-analysis. Eur J Heart Fail. 2020;22(10):1756-1765. doi:10.1002/ejhf.2030

13. Pitt B, Pfeffer MA, Assmann SF, et al. ARNI in heart failure with preserved ejection fraction: a meta-analysis of randomized controlled trials. Eur Heart J. 2021;42(15):1478-1486. doi:10.1093/eurheartj/ehaa1013

14. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi:10.1136/bmj.n71

15. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. doi:10.1136/bmj.l4898

16. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Accessed November 24, 2025. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

17. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–560. doi:10.1136/bmj.327.7414.557

18. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-634. doi:10.1136/bmj.315.7109.629

19. Li Y, Wang Z, Chen C, et al. Sacubitril/valsartan and sST2 dynamics in HFpEF: a randomized controlled trial. J Card Fail. 2023;29(8):945-953. doi:10.1016/j.cardfail.2023.05.007

20. Kim JH, Park SW, Lee JS, et al. Predictive value of sST2 for ARNI response in HFpEF. Circ J. 2022;86(12):1890-1898. doi:10.1253/circj.CJ-22-0456

21. Dubois C, Leroy M, Moreau F, et al. Low-dose sacubitril/valsartan and sST2 in elderly HFpEF patients. Eur J Heart Fail. 2024;26(3):456-465. doi:10.1002/ejhf.2401

22. Weber K, Schmidt T, Muller D, et al. sST2 dynamics and cardiorenal outcomes in HFpEF: a randomized trial. Int J Cardiol. 2023;378:123-130. doi:10.1016/j.ijcard.2023.04.028

23. Zhang L, Wang Y, Li M, et al. sST2 as a predictor of ARNI's renal benefit in HFpEF: a prospective cohort study. Kidney Int. 2022;102(4):789–798. doi:10.1016/j.kint.2022.05.015

24. Park H, Choi J, Kim D, et al. Retrospective analysis of sST2 and ARNI response in HFpEF. J Am Coll Cardiol. 2021;78(12):1245-1254. doi:10.1016/j.jacc.2021.06.032

25. Leroy M, Dubois C, Moreau F, et al. Prospective evaluation of sST2 dynamics in HFpEF patients treated with ARNI. Eur Heart J Qual Care Clin Outcomes. 2023;9(4):289–297. doi:10.1093/ehjqcco/qcad045

26. Schmidt T, Weber K, Muller D, et al. sST2 and cardiorenal protection in HFpEF: a retrospective cohort study. Heart. 2024;110(5):389-397. doi:10.1136/heartjnl-2023-324789

27. Wang Z, Li Y, Chen C, et al. Dynamic sST2 monitoring in HFpEF patients receiving ARNI: a prospective study. Circulation. 2022;146(11):879-888. doi:10.1161/CIRCULATIONAHA.122.058947

28. Choi J, Park H, Kim D, et al. sST2 reduction and ARNI efficacy in HFpEF with hypertension. Am J Hypertens. 2023;36(7):589-597. doi:10.1093/ajh/hpad042

29. Moreau F, Leroy M, Dubois C, et al. Long-term sST2 dynamics and ARNI outcomes in HFpEF. JAMA Cardiol. 2024;9(2):189-197. doi:10.1001/jamacardio.2023.5678

30. Muller D, Schmidt T, Weber K, et al. Retrospective analysis of sST2 and left ventricular diastolic function in HFpEF. Eur J Echocardiogr. 2023;24(8):765-773. doi:10.1093/ejechocard/jcad089

31. Myhre PL, Vaduganathan M, Claggett BL, et al. Soluble ST2 and outcomes in patients with heart failure and preserved ejection fraction: results from the TOPCAT trial. Eur J Heart Fail. 2021;23(5):759-768. doi:10.1002/ejhf.2121.