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ORIGINAL RESEARCH

Stroke in Heart Failure With Reduced Ejection Fraction

Systematic Review and Meta-Analysis of Randomized Trials

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ABSTRACT

BACKGROUND Patients with heart failure with reduced ejection fraction (HFrEF) have a heightened stroke risk. However, stroke as an endpoint in heart failure trials remains under-reported.

OBJECTIVES The authors sought to define the incidence, characteristics, predictors, modifier treatments, and prognostic impact of stroke in patients with HFrEF who were enrolled in randomized controlled trials (RCTs).

METHODS The authors systematically reviewed MEDLINE for RCTs of pharmacologic and nonpharmacologic treatments in HFrEF. The annualized stroke incidence was the primary outcome. Subgroup analyses and meta-regressions were performed to determine the baseline modulating characteristics and to assess the association of stroke with other clinical outcomes.

RESULTS Of 7,104 records, 188 RCTs fulfilled inclusion criteria for the systematic review. Of these, 158 studies (84.0%) did not report stroke outcomes and were excluded from the meta-analysis, leading to a final cohort of 30 studies, with 61 arms and 75,327 patients. Stroke incidence was 1.1% (95% CI: 0.9%-1.3%; I^2: 74%) with high heterogeneity across trials. Higher NYHA functional class ($P < 0.001$), lower systolic blood pressure ($P < 0.001$), diuretic use ($P = 0.001$), and diabetes ($P < 0.001$) were associated with stroke. No association of renin-angiotensin-aldosterone inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and transcatheter mitral valve replacement with stroke was observed. Stroke was associated with higher risk of all-cause and cardiovascular mortality, heart failure hospitalization and acute coronary syndromes ($P < 0.001$ for all).

CONCLUSIONS Stroke was reported in a vast minority of HFrEF RCTs with heterogeneous definitions and no reference to underlying mechanisms. Despite under-reporting, stroke incidence is non-negligible. Stroke is associated with HFrEF-specific characteristics and outcomes, whereas it is not impacted by current HFrEF treatments. There is a need for dedicated research into preventive strategies and effective treatments to address this debilitating and deadly comorbidity. (Stroke Events in Heart Failure With Reduced Ejection Fraction–A Systematic Review and Meta-Analysis of Pharmacologic Randomized Trial; CRD42023418422) (JACC Heart Fail. 2025;■:■–■) © 2025 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

ICD = implantable cardioverter-defibrillator

LVEF = left ventricular ejection fraction

MRA = mineralocorticoid receptor antagonist

RAASi = renin-angiotensin-aldosterone system inhibitor

RCT = randomized controlled trial

SGLT2i = sodium glucose cotransporter-2 inhibitor

TMVR = transcatheter mitral valve replacement

Patients with heart failure with reduced ejection fraction (HFrEF) have a heightened risk of thromboembolic events.[1-3] The risk of ischemic stroke is 2 to 3 times higher in patients with heart failure (HF) than in those without HF,[4,5] and patients with stroke and HF have higher mortality rates, more severe neurologic deficits, and longer hospital stays than those without HF.[6] The underlying pathophysiology is complex and multifactorial, comprising prothrombotic comorbidities (atrial fibrillation, vascular disease, diabetes, hypertension, etc) and direct mechanisms (intracardiac blood stasis directly related to atrial and ventricular systolic dysfunction, abnormalities of the endocardial wall, direct activation of thrombin-related pathways, and rheological abnormalities secondary to chronic neurohormonal activation).[3,7]

Despite this clinical burden reported by real-world studies, ischemic stroke as an endpoint in HF trials remains under-reported and its clinical relevance appears underestimated. Moreover, despite a rationale for the potential impact of HF-modifying drugs on stroke events, this hypothesis remains underexplored, likely due to the limited power of individual studies. We designed a systematic review and meta-analysis of randomized controlled trials (RCTs) enrolling patients with HFrEF to define the incidence, characteristics, clinical predictors, and prognostic impact of stroke as well as the effect of HF treatments on the risk of stroke in HFrEF.

METHODS

STUDY DESIGN. For this systematic review and meta-analysis, the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement guidelines were followed.[8] The original study protocol was prospectively registered in PROSPERO (CRD42023418422). The primary aim of this study was to assess the incidence, characteristics, clinical predictors, modifier treatments and prognostic impact of stroke events in patients affected by HFrEF enrolled in HFrEF RCTs. The secondary aim was to assess the frequency of stroke reporting in RCTs.

All randomized trials in HFrEF were considered for inclusion in the systematic review. For drug studies, only placebo-controlled or active arm-controlled studies were included, whereas for nonpharmacologic trials standard-of-care (SoC) controlled studies were also allowed. Studies were included if they were enrolling adult patients (≥18 years of age) with HFrEF exclusively, and if they were enrolling more than 300 patients (considering the low prevalence of stroke events). Studies were excluded if they were including patients in the acute nonstabilized phase of HF or HF patients with preserved ejection fraction.

Among included studies, only those reporting stroke outcomes were included in the meta-analysis.

STUDY OUTCOMES. The incidence of ischemic stroke was the primary outcome. When the etiology of stroke was not reported, the study-specific stroke definition was adopted.

The prespecified variables tested as potential predictors of incident stroke were demographics, body mass index (BMI), history of atrial fibrillation, prior stroke, ischemic cardiomyopathy, diabetes, hypertension, vascular disease, prior myocardial infarction (MI), left ventricular ejection fraction (LVEF), NYHA functional class, implantable cardioverter-defibrillator (ICD), systolic blood pressure, HF treatments, and anticoagulation. The association between incident stroke and all-cause mortality, cardiovascular mortality, HF hospitalization, and acute coronary syndromes (ACS) was evaluated.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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DATABASE SEARCH, STUDY SELECTION, AND DATA EXTRACTION. Published trials from MEDLINE/PubMed were identified from inception to the April 18, 2023. The full search strategy is detailed in the Supplemental Methods. The reference lists of selected articles were also searched manually to identify additional eligible studies. No language restrictions were applied during the search phase.

Two researchers (F.S. and D.M.) independently searched for studies fulfilling the criteria for inclusion in the systematic review in a 2-stage process, firstly using the title and abstracts of papers, and secondly using the full text for those papers that appeared to fulfil the criteria for inclusion. When the study outcome was not reported in the main paper, all secondary published analysis were searched in the MEDLINE/PubMed database. The reasons for excluding studies in this second phase were recorded. Randomized trials fulfilling all inclusion criteria but not reporting the study outcome were specifically noted to provide a measure of under-reporting of stroke outcome in HFrEF trials. The 2 researchers' results were compared and, if discrepancies occurred, these were discussed. If agreement was not reached, a third researcher (G.G.) was involved to reach a consensus.

Data about the studies included were extracted onto a predefined database. A full list of the included relevant baseline characteristics and the prespecified outcomes is reported in the Supplemental Methods. Information to assist the assessment of risk of bias in study design and execution was also extracted.

RISK OF BIAS ASSESSMENT. The quality of included studies was independently appraised by 2 reviewers with disagreements resolved by consensus. For each study, the risk of bias (low, some concerns, or high) for randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selective reporting was evaluated, in keeping with the Cochrane Collaboration approach.

Small study effect was estimated visually by funnel plots. No relevant small study effect was observed, thus excluding significant publication bias. Modest asymmetry was noted likely due to the low stroke incidence rate.[9] Details are shown in Supplemental Figure 1.

DATA SYNTHESIS AND ANALYSIS. The analysis was at study-arm level and by aggregated data. Any outcome of interest reported by each study was included and graphically displayed by forest plots. The incidence of clinical outcomes was annualized based on the reported mean/median study specific-follow-up and expressed as annualized incidence (%). Statistical pooling for the incidence of the primary outcome was performed using logit transformed proportions and reported as the pooled proportion with 95% CI applying the inverse transformation. Sensitivity analyses to assess the impact of different stroke definitions on the incidence of the primary outcome were conducted. The association of treatment categories—beta-blocker, renin-angiotensin-aldosterone system inhibitor (RAASi), mineralocorticoid receptor antagonist (MRA), sodium-glucose cotransporter 2 inhibitor (SGLT2i), diuretics, oral inotropes, rhythm-control agents, antithrombotic drugs, ICD, and transcatheter mitral valve replacement (TMVR)—with the primary outcome assessed among placebo-controlled or SoC-controlled studies by pooling the ORs for stroke using a binary random effects model and computing risk estimates with 95% CI. Meta-analysis was conducted when at least 2 studies for a given treatment category were available.

Subgroup analyses and meta-regressions of the primary outcome were performed to determine whether the incidence of stroke was modulated by the prespecified factors. Meta-regressions were also performed to assess whether stroke was associated with the incidence of all-cause mortality, cardiovascular mortality, HF hospitalization, and ACS. The Bonferroni correction for multiple testing was adopted to set the level of statistical significance.

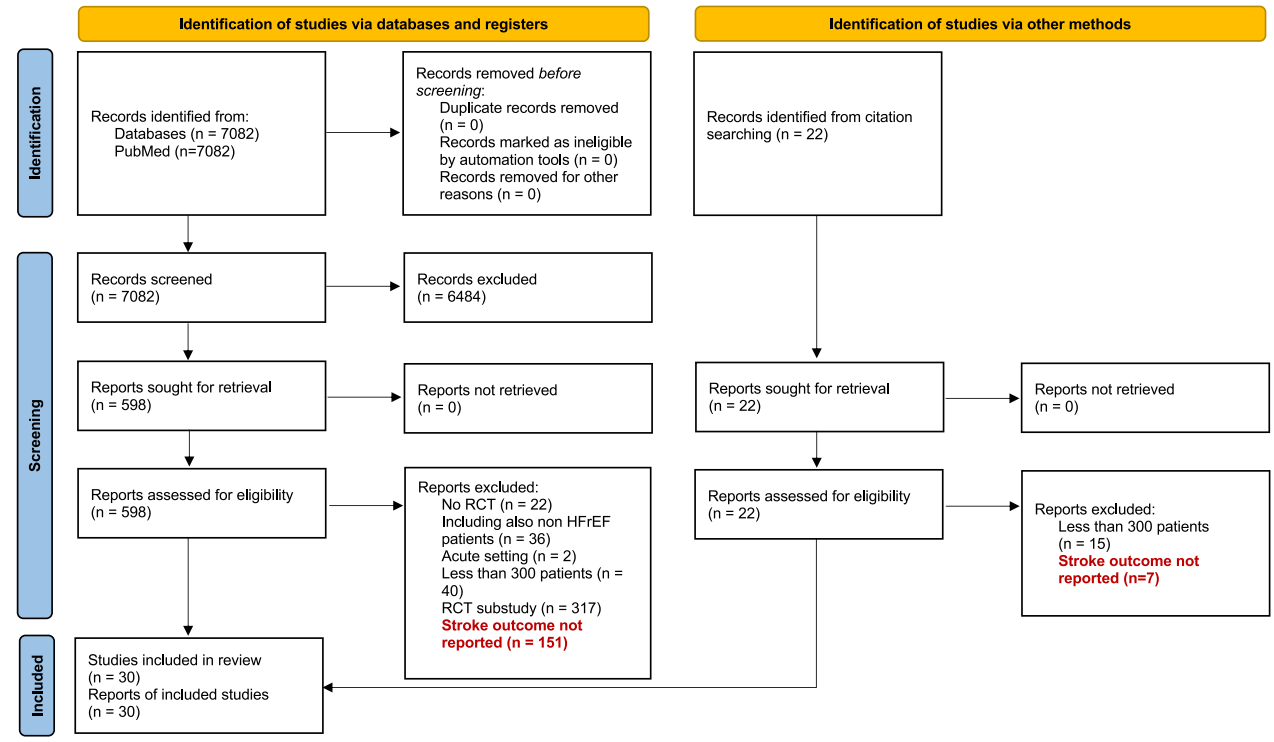
A sensitivity analysis was performed to assess whether serious adverse events (SAEs) reporting consistently captures stroke outcomes by assessing the differences in stroke reported as a study outcome or as an SAE. We also assessed the temporal trends of stroke as an SAE as the rates of background HF medications increased. Finally, we performed a sensitivity analysis to confirm the association of treatment categories with stroke using SAE data when reported.

The hypothesis of statistical heterogeneity was tested by means of the Cochrane Q statistic and I^2 values. I^2 values of <25%, 50%, or more than 50% indicated low, moderate, or substantial heterogeneity, respectively. Statistical 2-sided significance was set at $P < 0.05$. Statistical analyses were conducted with Stata 18 (StataCorp).

RESULTS

Of the 7,104 records retrieved, 188 studies fulfilled the inclusion criteria for systematic review. Of these, 158 studies (84.0%) did not report on stroke outcomes

FIGURE 1 Flowchart of the Study Selection Process



Selection process for the studies included in the systematic review and meta-analysis. Reprinted with permission of Page et al.[24] HFrEF = heart failure with reduced ejection fraction; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT = randomized controlled trial.

and were excluded from the meta-analysis, leading to a final cohort of 30 studies. The consort diagram is shown in **Figure 1**. The bias assessment for each RCT is shown in Supplemental Figure 2. Overall, 13 studies were considered at low risk of bias, 17 showed some concerns, and no studies were at high risk, based on Cochrane Collaboration guidelines. The PRISMA checklist is provided in the Supplemental Results.

MAIN CHARACTERISTICS OF INCLUDED STUDIES. Supplemental Tables 1 and 2 show the main characteristics of each RCT. The aggregated study and clinical characteristics are summarized in **Tables 1 and 2**.

Overall, 30 studies with 61 arms and 75,327 patients were included. Of these, 25 (83.3%) investigated drug treatments and 5 (16.7%) nonpharmacologic treatments. Eighteen (60%) studies were placebo-controlled, 7 (23.3%) active-treatment controlled, and 5 (16.7%) SoC-controlled. Median follow-up was 2 years (Q1-Q3: 1.5-3.1 years).

At the study-arm level, the median number of patients was 1,015 per study (Q1-Q3: 316-1.515), male sex prevalence was 77% (Q1-Q3: 72%-80%), and median age was 64 years (Q1-Q3: 62-66 years). Ischemic cardiomyopathy was prevalent (median: 62%; Q1-Q3: 55%-69%), median LVEF was 28% (Q1-Q3: 25%-31%), and median NYHA functional class was 3 (range: 2-3). Atrial fibrillation was common (median: 27%; Q1-Q3: 16%-34%) and a history of prior stroke was reported in 8% (Q1-Q3: 8%-10%). RAASi (median: 91%; Q1-Q3: 87%-99%), and beta-blockers (median: 81%; Q1-Q3: 54%-90%) were highly represented, and 27% (Q1-Q3: 15%-38%) were on any anticoagulation treatment.

PRIMARY ENDPOINT. The study level definitions for the stroke outcome are reported in Supplemental Table 3. Overall, stroke definitions were heterogeneous, with approximately half of the studies (n = 14) not publishing a per protocol stroke definition. Six studies adopted a combined outcome of fatal and

TABLE 1 Summary of Study Characteristics

Study level	
Included studies	30
Patients at study level	2,153 (621-2,956)
Year of study publication	1991-2022
Follow-up length, y	2 (1.5-3.1)
Studies with ≥2 arms	1 (3.3)
Control type	
Placebo-controlled	18 (60)
Active-arm controlled	7 (23.3)
SoC[a]	5 (16.7)
Study drug/treatment	
Pharmacologic	25 (83.3)
Beta-blocker	3 (10)
RAASi	10 (33.3)
MRA	3 (10)
OAC	2 (6.7)
Other	7 (23.3)
Nonpharmacologic	5 (16.7)
Implantable cardioverted defibrillator[b]	2 (6.7)
TMVR	2 (6.7)
Atrial fibrillation ablation	1 (3.3)
Arm level	
Study arms	61
Patients at arm level	1,015 (316-1,515)
Study drug/treatment	
Pharmacologic	33 (54.1)
Beta-blocker	4 (6.6)
RAASi	16 (26.2)
MRA	3 (4.9)
OAC	2 (3.3)
Other	8 (13.1)
Nonpharmacologic	5 (8.2)
Implantable cardioverted defibrillator[b]	2 (3.3)
TMVR	2 (3.3)
Atrial fibrillation ablation	1 (1.6)
Placebo	18 (29.5)
SoC[a]	5 (8.2)

Values are n, median (Q1-Q3), or n (%), unless otherwise indicated. [a]Only SoC-controlled nonpharmacologic randomized controlled trials (RCTs) could be included. [b]One RCT of implantable cardioverter-defibrillator without defibrillator testing vs standard implantation.

MRA = mineralocorticoid receptor antagonist; OAC = oral anticoagulant; RAASi = renin-angiotensin-aldosterone system inhibitor; SoC = standard of care; TMVR = transcatheter mitral valve replacement.

TABLE 2 Summary of Clinical Characteristics of the Cohorts Included in the Meta-Analysis

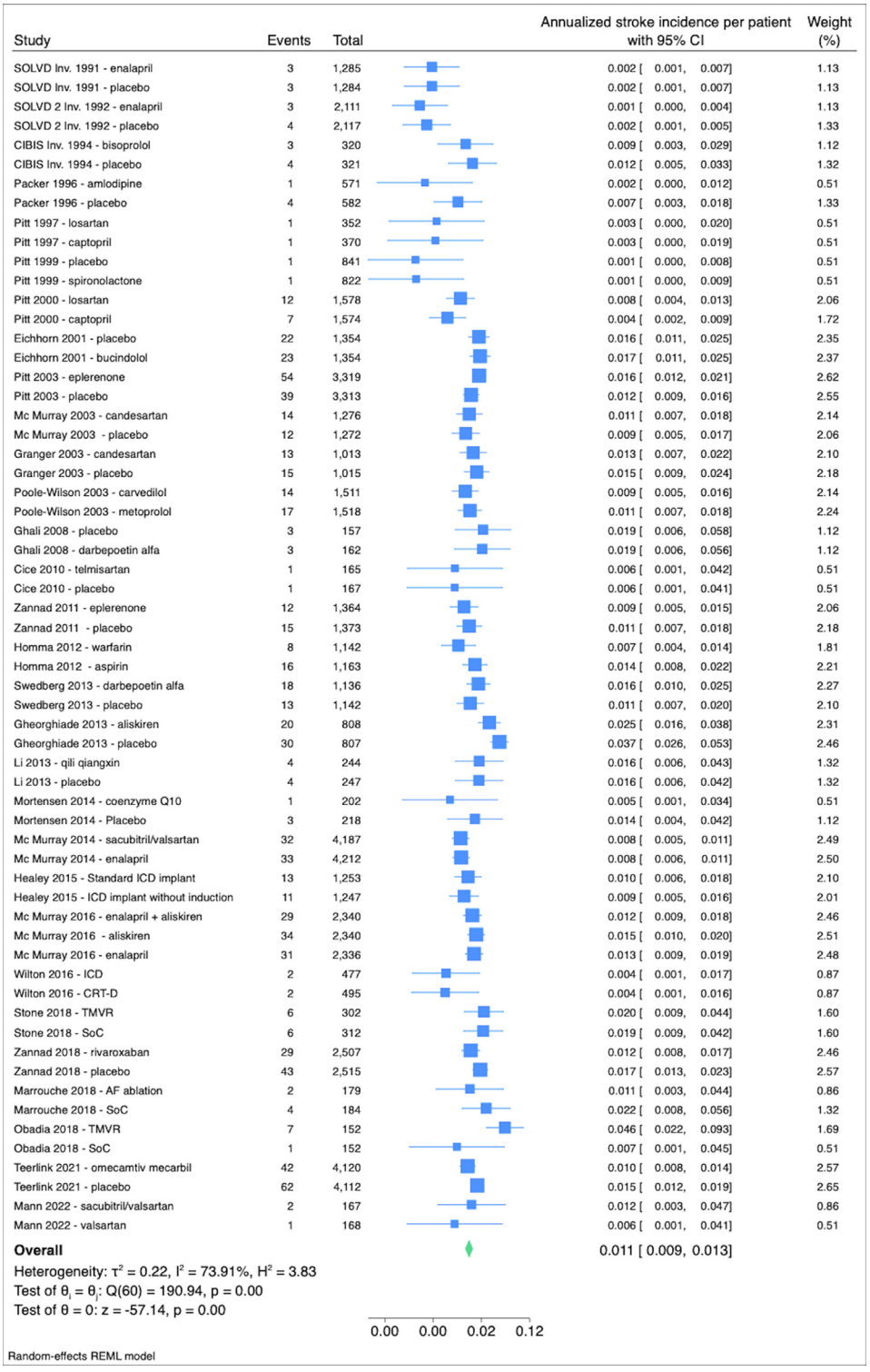
	Median (Q1-Q3)	Study Arms, n (%)
Anthropometrics		
Male	77 (72-80)	61 (100)
Age, y	64 (62-66)	61 (100)
BMI, kg/m^2	27 (27-28)	30 (49.2)
Race		
White	82 (70-87)	41 (67.2)
Black	5 (2-11)	41 (67.2)
Asian	17 (11-25)	39 (63.9)
Clinical features		
HF etiology		
Ischemic	62 (55-69)	53 (86.9)
Nonischemic	37 (31-45)	49 (80.3)
NYHA functional class		
I	3 (2-3)	57 (93.4)
II	44 (32-56)	51 (83.6)
III	48 (33-67)	51 (83.6)
IV	3 (2-8)	51 (83.6)
Prior HF hospitalization	59 (36-66)	19 (31.1)
ICD	15 (13-32)	27 (44.3)
CRT	6 (5-27)	19 (30.2)
SBP, mm Hg	123 (119-125)	51 (83.6)
NT-proBNP, ng/L	1,818 (1,260-2,349)	23 (37.7)
LVEF, %	28 (25-31)	61 (100)
Dyslipidemia	41 (38-46)	14 (23.0)
Hypertension	61 (50-71)	49 (80.3)
Smoke	23 (16-33)	18 (29.5)
Diabetes	30 (25-37)	53 (86.9)
CKD	20 (13-33)	10 (16.4)
eGFR, mL/min/1.73 m^2	66 (48-74)	17 (27.0)
Previous MI	51 (41-58)	39 (63.9)
Prior coronary revascularization	42 (40-47)	14 (23.0)
Atrial fibrillation	27 (16-34)	49 (80.3)
Prior stroke	8 (8-10)	27 (44.3)
HF treatments		
RAASi	91 (87-99)	39 (63.9)
ACEI	91 (70-99)	32 (52.5)
ARB	19 (9-78)	18 (29.5)
ARNI	19 (14-39)	4
MRA	36 (17-56)	39 (61.9)
Beta-blocker	81 (54-90)	49 (77.8)
SGLT2i	0 (0-0)	2 (3.3)
Diuretic agent	89 (80-94)	47 (77.0)
Digoxin	49 (31-60)	43 (70.5)
Antiarrhythmic	14 (12-19)	24 (39.3)
Anticoagulation	27 (15-38)	20 (32.8)
VKA	30 (22-38)	16 (26.2)
DOAC	50 (25-75)	2 (3.3)
Antiplatelet therapy	51 (37-59)	26 (42.6)

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BMI = body mass index; CKD = chronic kidney disease; CRT = cardiac resynchronization therapy; DOAC = direct oral anticoagulation; eGFR = estimated glomerular filtration rate; HF = heart failure; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SBP = systolic blood pressure; SGLT2i = sodium-glucose cotransporter 2 inhibitor; VKA = vitamin K antagonist; other abbreviations as in Table 1.

nonfatal strokes, with no reference to event etiology. Ischemic stroke was reported in 3 studies, and hemorrhagic stroke in 3 studies. Two studies reported both ischemic and hemorrhagic strokes. No data on the specific stroke mechanism were reported in any study. Two studies also included transient ischemic attack, and 3 studies used a broad cerebrovascular accident definition.

The pooled annualized stroke incidence was 1.1% (95% CI: 0.9%-1.3%), with high heterogeneity among studies ($I^2 = 74\%$) (Figure 2). In sensitivity analyses by

FIGURE 2 Summary Forest Plot for the Primary Study Endpoint of Annualized Stroke Incidence



Studies listed in the forest plot are referenced in the Supplemental References. AF = atrial fibrillation; CRT-D = cardiac resynchronization therapy-defibrillator; ICD = implantable cardioverter-defibrillator; SoC = standard of care; TMVR = transcatheter mitral valve replacement.

stroke definition, the annualized stroke incidence remained similar for studies reporting ischemic stroke (1.0% [95% CI: 0.7%-1.4%]), with reduced albeit still moderate heterogeneity (I^2 = 46%) (Supplemental Figure 3). The annualized incidence of hemorrhagic stroke was low (0.21% [95% CI: 0.09%-0.49%]; I^2 = 48%) (Supplemental Figure 4).

Among studies reporting a study-level definition of the combined occurrence of fatal and nonfatal strokes, the annualized stroke incidence remained similar, and heterogeneity was reduced (1.1% [95% CI: 1.0%-1.4%]; I^2 = 41%).

The pooled annualized incidence of several stroke definitions with the related 95% CIs and estimated heterogeneity are reported in Supplemental Table 4.

In subgroup analyses, no heterogeneity in stroke incidence was observed according to the type of treatment arm (drug vs nonpharmacologic vs placebo vs SoC) (Supplemental Figure 5), whereas stroke incidence was higher among studies conducted after 2011 (median study publication year, test for subgroup differences; $P < 0.001$) (**Figure 3**).

PREDICTORS OF INCIDENT STROKE. At meta-regression analysis, higher NYHA functional class (beta coefficient of 0.5797; $P < 0.001$; R^2 = 40%), lower systolic blood pressure (beta coefficient of −0.0472; $P < 0.001$; R^2 = 22%), diabetes (beta coefficient of 0.0362; $P < 0.001$; R^2 = 34%), and diuretic use (beta coefficient of 0.0180; $P = 0.001$; R^2 = 27%) (**Table 3**, **Figure 4**) were associated with stroke incidence. Atrial fibrillation, N-terminal pro-B-type natriuretic peptide (NT-proBNP), ischemic cardiomyopathy, prior MI, LVEF, and hypertension were associated with stroke incidence, although losing significance after Bonferroni correction. Sex, age, BMI, ICD, smoking history, and prior stroke were not associated with stroke incidence.

ASSOCIATION OF TREATMENT CATEGORIES WITH STROKE INCIDENCE. Among the tested treatment categories (beta-blocker, RAASi, MRA, SGLT2i, diuretic agents, oral inotropes, rhythm-control agents, antithrombotic drugs, ICD, and TMVR), only beta-blocker, RAASi, MRA, and TMVR had at least 2 RCTs comparing the active treatment with placebo/SoC for the outcome incident stroke and therefore underwent meta-analysis. No association of any treatment category with stroke incidence was observed (**Figure 5**, Supplemental Table 5).

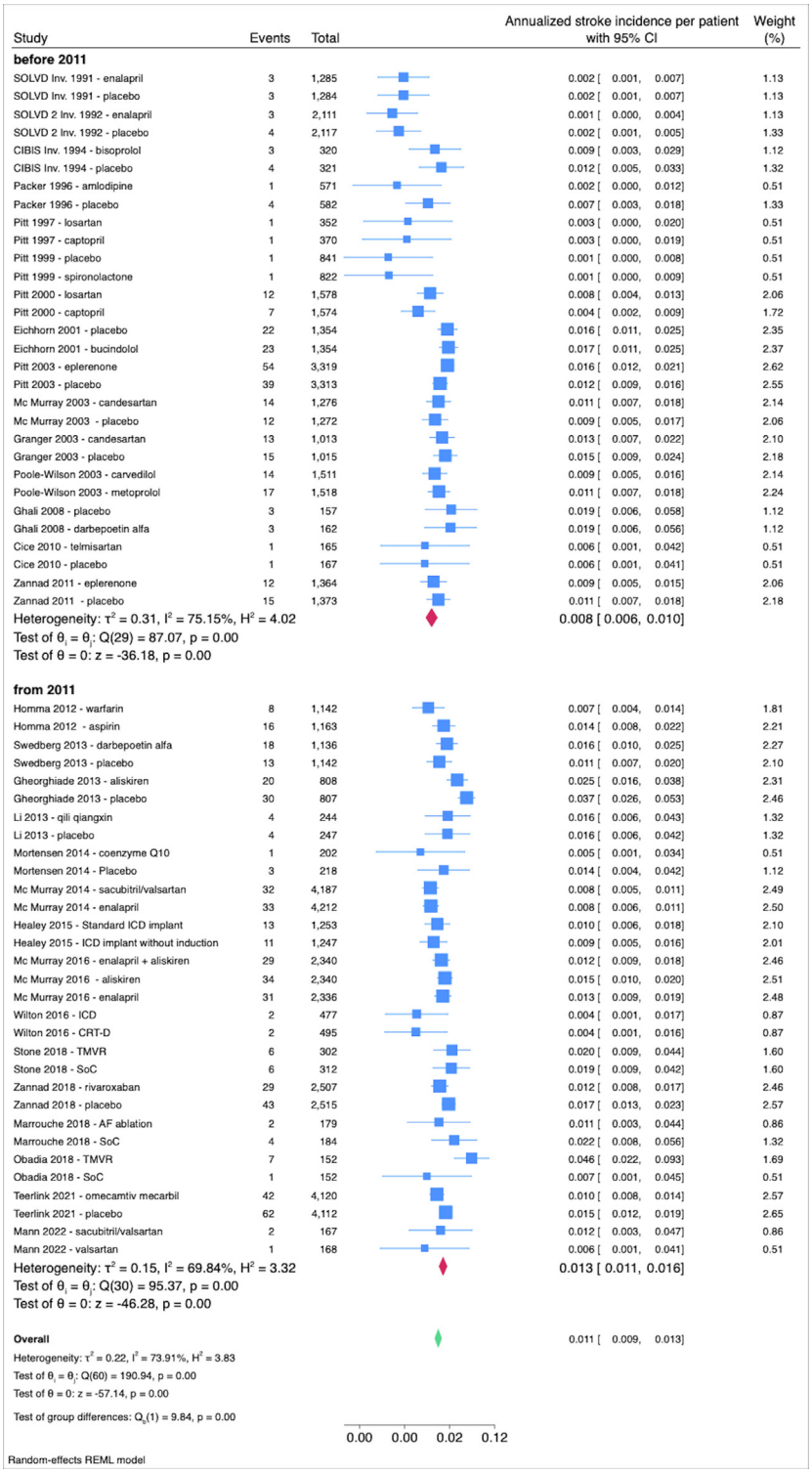
ASSOCIATION OF STROKE WITH CLINICAL OUTCOMES. At meta-regression analysis, stroke was associated with all-cause mortality (beta-coefficient of 0.6377; $P < 0.001$; R^2 = 22%), with cardiovascular mortality (beta coefficient of 0.4160; $P < 0.001$), with HF hospitalization (beta-coefficient of 0.6815; $P < 0.001$; R^2 = 42%), and with ACS (beta coefficient of 0.5986; $P < 0.001$; R^2 = 41%) (**Figure 6**, Supplemental Table 6).

STROKE IN SAE REPORTS. Stroke was reported as an SAE in 12 (38.7%) of the included studies. SAE stroke definitions were heterogeneous, with 8 studies reporting "stroke" data, 2 studies reporting "ischemic or hemorrhagic stroke" data, and 2 studies reporting a broad "cerebrovascular accident" and "nervous system disorders" definitions. The reported annualized incidence of stroke as an SAE or an outcome was inconsistent in 50% of the studies reporting both metrics, although with minimal variations (overall median difference: 0%; Q1-Q3: 0%-0.17%). When assessing temporal trends of stroke as an SAE, the incidence remained stable over the last 3 decades despite overall increasing rates of background HF medical treatments (P for interaction = 0.140) (Supplemental Figure 6). Finally, no association of any treatment category with stroke incidence was observed when also considering stroke incidence reported as an SAE (Supplemental Figure 7).

DISCUSSION

In this systematic review and meta-analysis including 75,327 patients with HFrEF who were enrolled in 61 arms of therapeutic RCTs, we sought to define the incidence, characteristics, and prognostic impact of stroke events in patients affected by HFrEF enrolled in HFrEF RCTs. The main findings and related potential implications can be summarized as follows (**Central Illustration**): 1) among eligible HFrEF RCTs, stroke events were reported in a vast minority (16.0%); in studies reporting stroke as outcome, the stroke definitions were often unavailable, heterogeneous, and reference to the underlying mechanisms (primary ischemic vs thromboembolic) were never available; 2) in the selected cohorts of RCTs, stroke occurred annually in 1.1%; although this highlights the challenges of designing RCTs that can capture treatment effects for this outcome, this event rate remains non-negligible on clinical grounds; 3) several characteristics of HFrEF severity were associated with stroke incidence, indirectly suggesting an HF-specific link, and pointing to the potential role of cardioembolic events as the prevalent cause of stroke in HFrEF; and 4) no association of current mainstay

FIGURE 3 Subgroup Analysis of Stroke Incidence According to Median Study Publication Year



Stroke incidence is reported according to median study publication year: before vs from 2011. Studies listed in the forest plot are referenced in the Supplemental Table 3. Abbreviations as in **Figure 2**.

HFrEF treatments—including neurohormonal inhibiting drugs and TMVR—with stroke incidence was observed, highlighting an unmet clinical need and the requirement for further dedicated research in this area.

HFrEF and stroke represent significant burdens on global health, with considerable overlap in their epidemiology and intricate pathophysiological links.[10-12] The intertwined nature of these conditions, comprised within the wider concept of "cardiocerebral syndrome" highlights the potential direct consequences of HF on brain,[1,2] encompassing a spectrum of injurious mechanisms from chronic hypoperfusion to silent brain lesions and debilitating clinical cardioembolic strokes. Based on this recognition, several consensus documents have been issued describing best practices in prevention, diagnosis, and management of stroke in HF patients.[3,11] However, current recommendations are informed by limited evidence and mostly rely on expert opinion because of the challenges in designing clinical studies on this complex topic. In this framework, our systematic review and meta-analysis provides several insights that may inform clinical practice and future research in this field.

First, we underscore the relevance of current gaps in stroke reporting in HFrEF RCTs. Of 188 RCTs on HFrEF treatments eligible for this systematic review, only 16.0% reported any sort of stroke outcome. Among this selected subgroup, approximately half of the studies did not provide any per protocol published stroke definition and only 2 studies reported both ischemic and hemorrhagic events. When available, stroke definitions were heterogeneous, in 1 case including transient ischemic attack and in 3 studies using a broad cerebrovascular accident definition. Importantly, no study adjudicated or reported the attributed mechanism of ischemic stroke, thus missing the opportunity to investigate the relative importance of cardioembolic events, more strictly related to the HFrEF physiology, as opposed to the events driven by large artery atherosclerosis. Although this highlights the challenges of adjudicating stroke mechanisms in clinical practice (ie, to differentiate a primary hemorrhagic stroke from a hemorrhagic evolution of a primary ischemic stroke, or to clearly identify a cardioembolic etiology), it also increases the importance of an effort to develop and to mandate tailored pragmatic definitions of granular stroke outcomes to be included in the protocols of HFrEF treatments RCTs.

TABLE 3 Meta-Regression of the Predictors of Incident Stroke

	Study Arms, N	Coefficient	Intercept	*P* Value	I^2, %	R^2, %
Male	61	0.0191	-3.0548	0.077	73	3
Age, y	61	0.0238	-6.0575	0.252	74	0
BMI, kg/m^2	31	0.1378	-5.0995	0.188	61	5
Ischemic cardiomyopathy	53	0.0180	-3.4237	0.036	73	5
NYHA functional class	55	0.5797	-5.9705	**<0.001**	66	40
ICD	27	0.0014	-4.3236	0.680	67	0
SBP, mm Hg	49	0.0472	1.2453	**0.001**	75	22
NT-proBNP, ng/L	23	0.0003	-4.5995	0.026	70	24
LVEF, %	61	0.0552	-6.1002	0.014	73	0.7
Hypertension	47	0.0096	-5.1290	0.028	74	4
Smoke	18	0.0059	-5.1711	0.619	80	0
Diabetes	53	0.0362	-5.6278	**<0.001**	67	34
Previous MI	39	0.0147	-3.8308	0.035	71	0
Atrial fibrillation	49	0.0128	-4.8743	0.011	72	16
Prior stroke	27	0.0123	-4.5681	0.648	31	0
Diuretic agents	45	0.0179	-6.0645	**0.001**	69	27

Significance level with Bonferroni correction $P < 0.0028$. **Bold** indicates findings above the level of significance set at $P < 0.003$ by the Bonferroni correction.

Abbreviations as in Table 2.

Second, in a broad sample representative of the HFrEF cohorts included in therapeutic RCTs, we found a pooled annualized stroke incidence of 1.1%. As a framework, annualized stroke incidence is at 0.13% in the general contemporary European population,[10] 0.29% in patients with controlled hypertension, 0.71% in those with uncontrolled hypertension,[13] and 1.3% to 1.4% in individuals with diabetes who are >65 years of age.[14] Regarding HFrEF cohorts, our observed data are somewhat lower, (although grossly consistent) with the numbers reported in real-world practice, likely reflecting the more selected RCTs populations. In a wide Danish nationwide cohort study representative of real-world epidemiology, the 1-year incidence of stroke was 1.4%.[15] Higher stroke rates in HF have been reported in those studies exploring incident HF populations; however, it is well-known how the risk of ischemic stroke is increased more than 5-fold in the first month after the diagnosis of HF,[16] which is a different setting from that of HFrEF RCTs that generally enroll optimally treated prevalent HF patients. From a practical standpoint, this number may inform the sample size calculation when designing RCTs powered for stroke outcomes in HFrEF cohorts. The heterogeneity in stroke incidence across RCTs was elevated, an observation partly explained by the difference in baseline HFrEF characteristics across studies. Meta-regression analysis identified higher NYHA

FIGURE 4 Meta-Regression of the Predictors of Incident Stroke

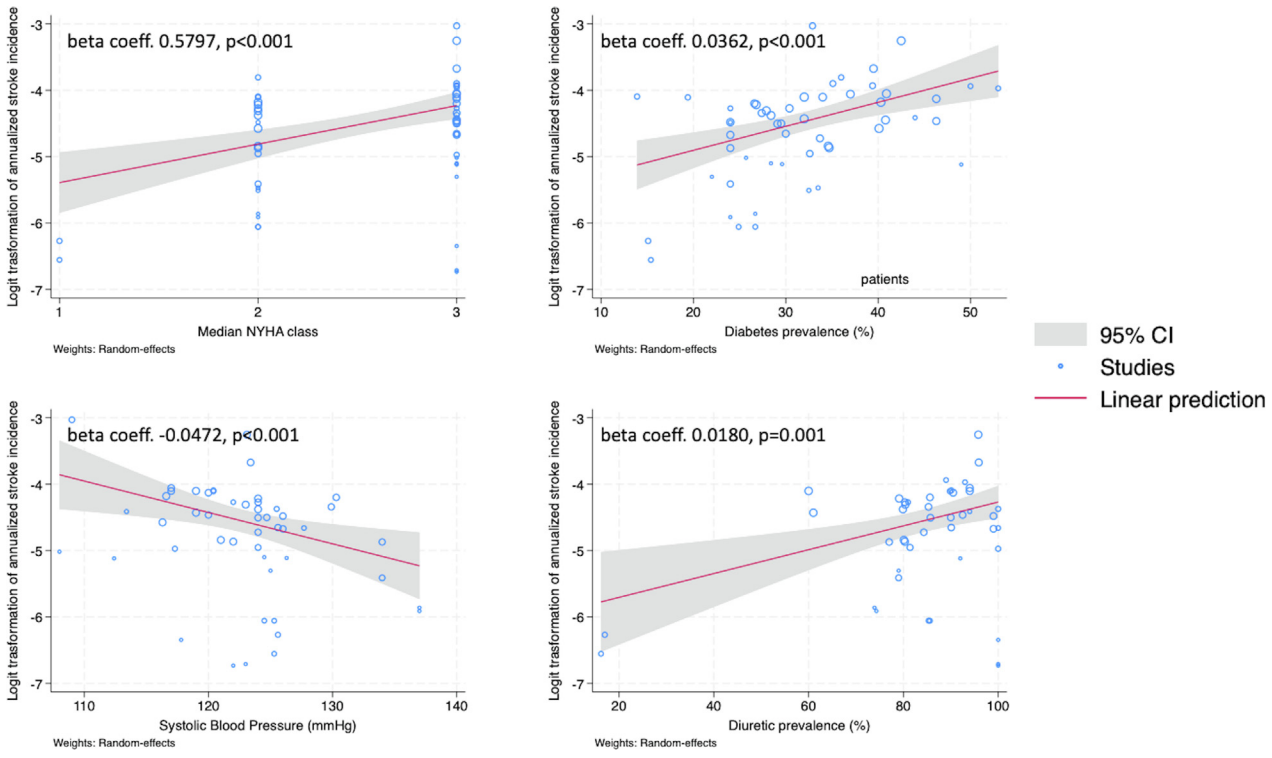
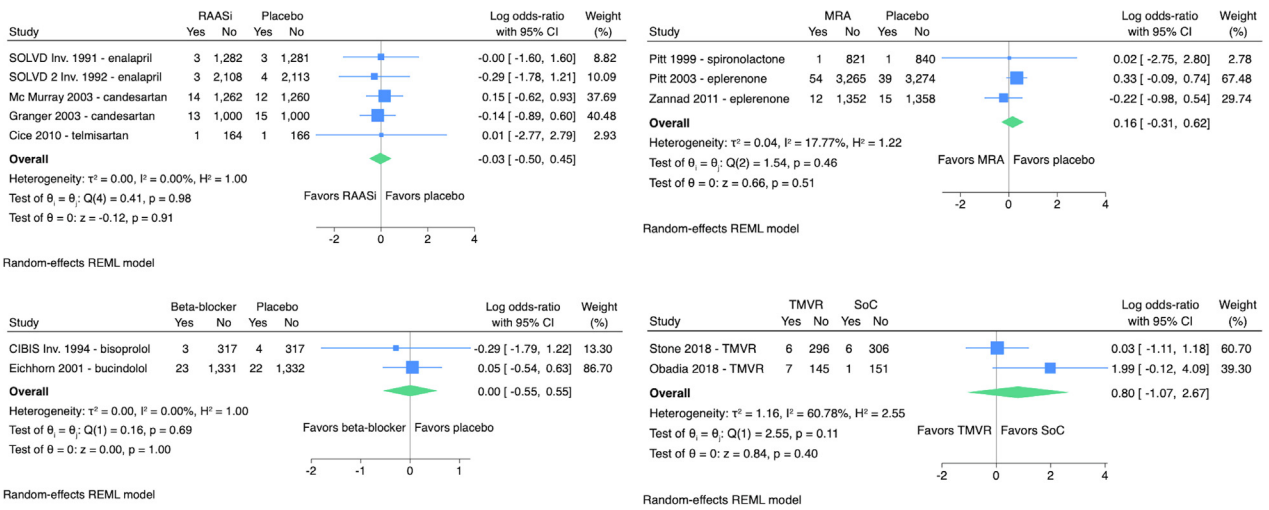
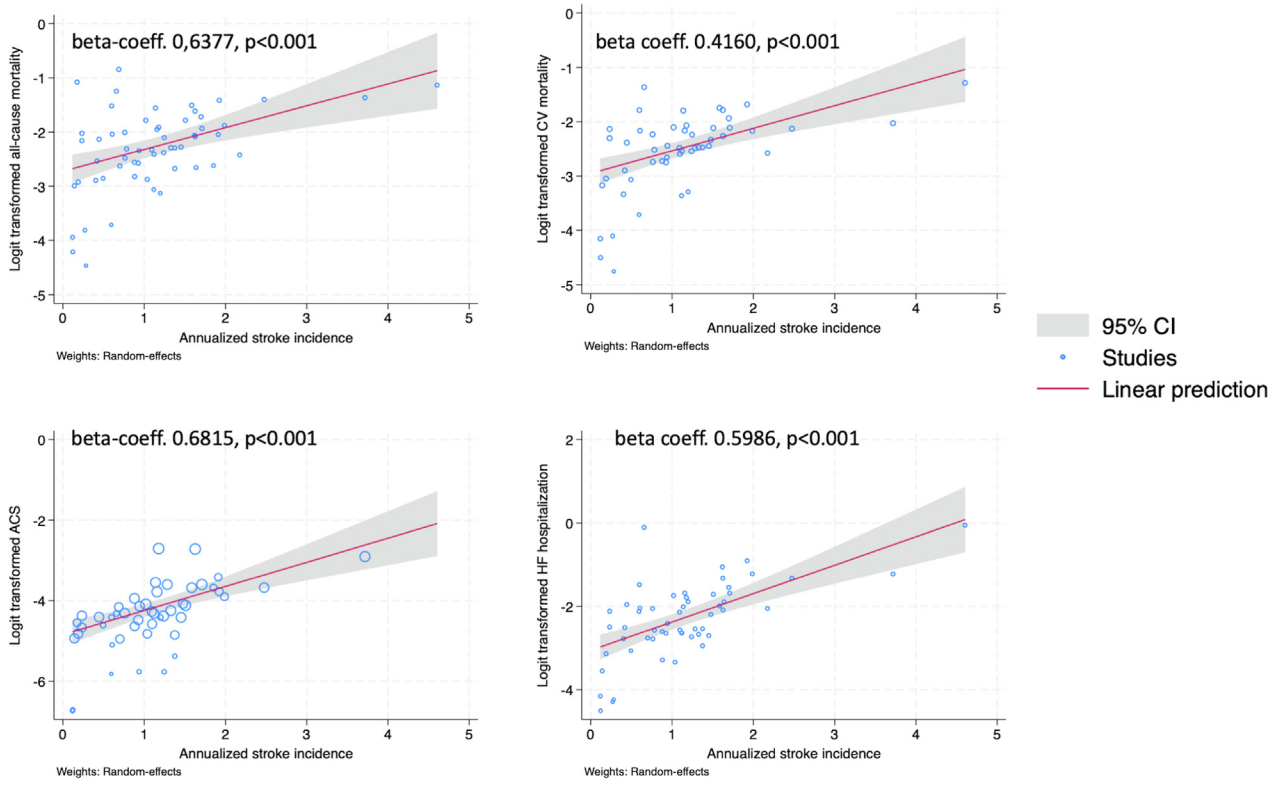


FIGURE 5 Forest Plots for the Association of Treatment Categories With Stroke Incidence in Placebo-Controlled or SoC-Controlled Studies



Studies listed in the forest plot are referenced in the Supplemental Tables 1 and 2. MRA = mineralocorticoid receptor antagonist; RAASi = renin-angiotensin-aldosterone system inhibitor; REML = restricted maximum likelihood; other abbreviations as in Figure 2.

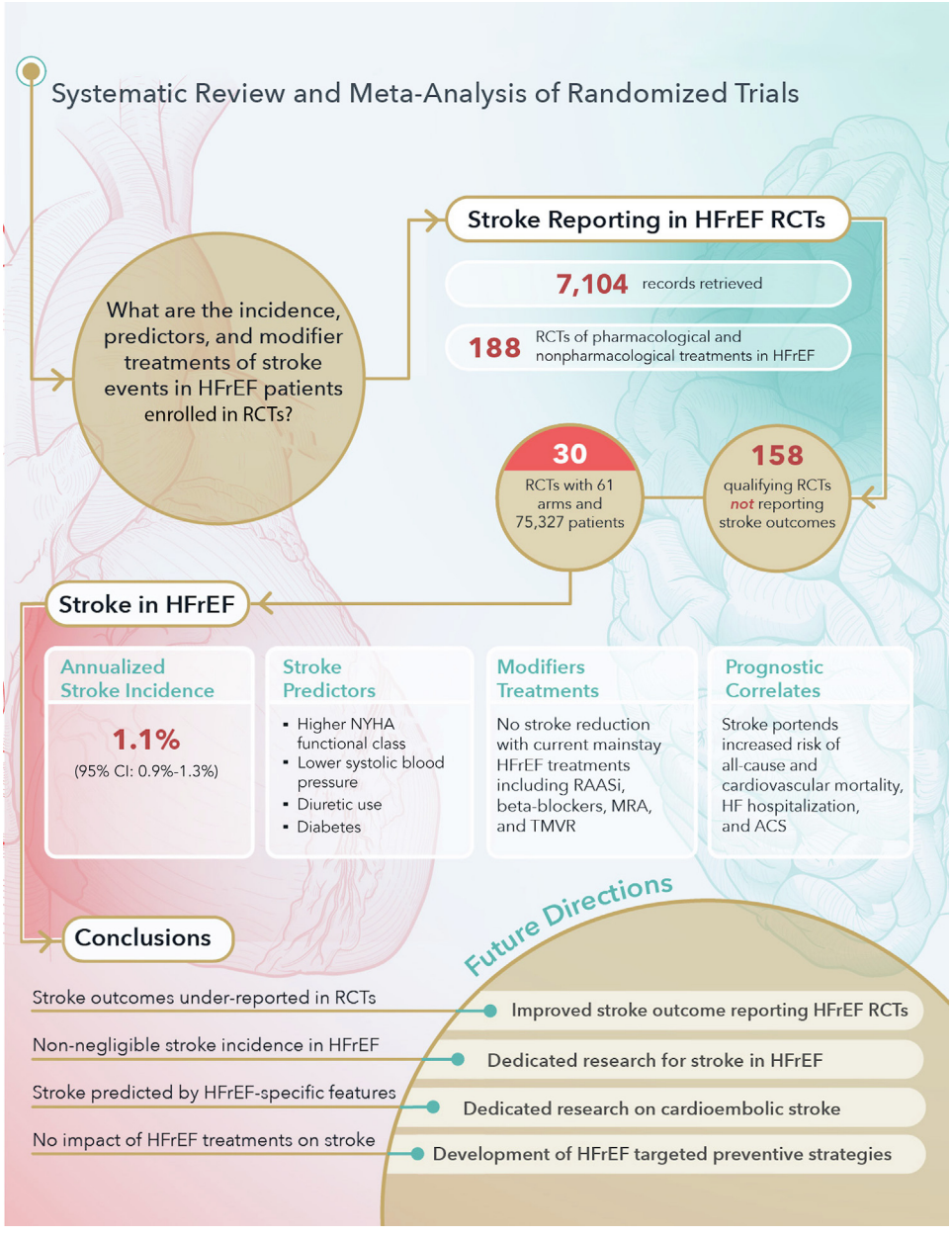
FIGURE 6 Meta-Regression of Stroke Incidence for All-Cause Mortality, CV Mortality, HF Hospitalization and ACS



ACS = acute coronary syndromes; CV = cardiovascular; HF = heart failure.

functional class, lower systolic blood pressure, diabetes, and diuretic use as the strongest baseline modulators of stroke incidence. Although suggesting that inclusion of higher-risk populations satisfying these criteria may be adopted to reduce sample size and improve study power in future dedicated RCTs, these observations also carry relevant clinical implications by identifying a subset of patients at higher risk of stroke. Our results are backed and reinforced by prior evidence identifying NYHA functional class and diabetes as strong correlates of stroke risk.[17,18] In a pooled patient-level cohort of 3 contemporary HFrEF RCTs, insulin-treated diabetes was associated with a 1.3-fold increase in stroke risk.[18] A simple score (S2I2N0-3 score) comprising insulin-treated diabetes, prior stroke history, and natriuretic peptides levels, effectively stratified the risk of stroke among HFrEF patients without atrial fibrillation, and patients in the highest score quintile had a similar risk of stroke to HFrEF patients with atrial fibrillation not receiving anticoagulation.[18] Our study aligns with these findings, highlighting the potential to identify a subset of HFrEF patients at higher stroke risk that might benefit from prophylactic anticoagulation. In our analysis, other established modulators of stroke risk including atrial fibrillation[19,20] and NT-proBNP[18] were associated with stroke outcomes ($P = 0.011$ and $P = 0.026$, respectively), although losing statistical significance after the Bonferroni correction. In the context of prior published reports, these results should not diminish the importance of these factors when stratifying the cardioembolic risk in HFrEF. We did not observe any association of stroke history with stroke incidence, a finding in contrast to prior published reports. We believe that the plausible explanation is analytical: only 13 studies (27 study arms) reported this information, and the median prevalence of stroke history was roughly uniform across studies

CENTRAL ILLUSTRATION Stroke in HFrEF



Gallone G, et al. JACC Heart Fail. 2025;■(■):■-■.

A systematic review and meta-analysis were conducted to define the incidence, clinical predictors, modifier treatments and prognostic impact of stroke events in patients with heart failure with reduced ejection fraction (HFrEF) who were enrolled in randomized controlled trials (RCTs). Despite frequent under-reporting of stroke outcomes in HFrEF RCTs, stroke incidence is non-negligible. Stroke is associated with HFrEF-specific characteristics and outcomes, whereas current HFrEF treatments do not appear to impact its incidence. There is a need for more comprehensive reporting of stroke outcomes in HFrEF RCTs and dedicated research into preventive strategies and effective treatments to address this ominous comorbidity. ACS = acute coronary syndrome; HF = heart failure; MRA = mineralocorticoid receptor antagonist; RAASi = renin-angiotensin-aldosterone system inhibitor; TMVR = transcatheter mitral valve replacement.

(median prevalence: 8%; Q1-Q3: 8%-10%) thus precluding meta-regression to capture the impact of this variable on stroke outcomes.

Third, despite the clinical relevance and the ominous consequences of cardioembolic stroke in HFrEF, no current evidence is available supporting any effective preventive strategy in this setting.[11] Oral anticoagulation in patients with HFrEF and sinus rhythm had no impact on mortality, and the reduction in stroke (HR: 0.66 [95% CI: 0.47-0.95]) was largely offset by increased bleedings.[21,22] We could not meta-analyze the use of anticoagulation in the per treatment categories analysis because a single placebo-controlled trial of anticoagulation satisfied the inclusion criteria (COMMANDER-HF [A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction, or Stroke in Participants with Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure]), and the other trial that included anticoagulation (WARCEF [Warfarin Versus Aspirin in Reduced Cardiac Ejection Fraction Trial]) had an active comparator (aspirin), thus precluding pooling with the COMMANDER-HF data. As intracardiac blood stasis (a central component in the pathogenesis of intracardiac thrombosis) is directly related to systolic dysfunction, there is a rationale to support a role for treatments that have an impact on ventricular positive remodeling on stroke prevention. However, this hypothesis was never proven in individual RCTs. In this meta-analysis, we found no association of neurohormonal-inhibiting drugs with stroke incidence, suggesting that the favorable disease-modifying effects on HFrEF natural history are unable to translate into a clinically significant reduced risk of cardioembolism at the population level. Although only few RCTs could be meta-analyzed for each treatment, the absence of any numerical treatment effect (pooled log-OR ranging from −0.03 for RAASi to +0.80 for TMVR) and the low heterogeneity across included RCTs suggest that this finding is unrelated to low sample size and is reliable. The association of some novel HFrEF treatments, including SGLT2i and omecamtiv mecarbil, could not be analyzed due to single/no eligible RCTs and remains to be addressed in future dedicated studies. In the phase III GALACTIC-HF (Global Approach to Lowering Adverse Cardiac Outcomes through Improving Contractility in Heart Failure) trial,[23] omecamtiv mecarbil was associated with a significant reduction in the safety stroke outcome (HR: 0.68 [95% CI: 0.51-0.91]).

Our meta-analysis representing the largest comprehensive evidence on the association of HFrEF treatments with stroke outcomes highlights a relevant unmet clinical need and emphasizes the need for dedicated RCTs to identify effective preventive strategies of this ominous and non-negligible comorbidity of HFrEF.

STUDY LIMITATIONS. First, this is a study-level meta-analysis, and the findings provide mean study-level effects. The median NYHA functional class of the studies included in the meta-analysis is higher than the average NYHA functional class of most stable HF trials. Thus, stroke incidence in stable HFrEF patients with lower NYHA functional classes may be somewhat lower than the reported mean study-level effect. Second, meta-regression was adopted to assess the association between study-level covariates and outcome. Even if many RCTs informed the analyses and the results are plausible, the associations between average patient characteristics and the pooled treatment effect may not always reflect true associations between the individual patient-level characteristics and treatment effect.

Third, a dynamic risk stratification accounting for the patient's trajectory rather than focusing on a single timepoint assessment might provide more actionable insights for risk stratification. Unfortunately, these data were not available in any of the included studies.

Fourth, despite the primary focus of this systematic review and meta-analysis being ischemic stroke, most studies did not provide separate data for ischemic and hemorrhagic stroke. However, this is unlikely to have significantly affected study results and conclusions as primary hemorrhagic stroke represent a vast minority of the overall stroke epidemiology in HFrEF, as highlighted in sensitivity analysis and prior published reports.[18] Moreover, results remained consistent in analyses restricted to RCTs reporting ischemic stroke.

Finally, we could not assess the incidence and relevance of cardioembolic stroke because the etiology of ischemic stroke was not reported in any of the included studies. This is inherently related to the reported data from current RCTs and identifies an area for improvement in research methodology, also to enhance understanding of stroke pathophysiology in HFrEF.

CONCLUSIONS

Despite frequent under-reporting of stroke outcomes in HFrEF RCTs, stroke incidence is non-negligible. Stroke is associated with HFrEF-specific characteristics and outcomes, whereas current HFrEF treatments do not appear to impact its incidence. There is a need for more comprehensive reporting of stroke outcomes in HFrEF RCTs and dedicated research into preventive strategies and effective treatments to address this ominous comorbidity.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients with HFrEF have a heightened risk of stroke. Several characteristics of HFrEF severity predict stroke incidence, suggesting a disease-specific link and pointing at the potential role of cardioembolic events as the prevalent cause of stroke in HFrEF.

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Despite the ominous consequences of cardioembolic stroke in HFrEF, no current evidence is available supporting any effective preventive strategy in this setting, including oral anticoagulation (in patients in sinus rhythm), neurohormonal inhibiting drugs, and TMVR.

TRANSLATIONAL OUTLOOK 1: Despite the clinical relevance of stroke among patients with HFrEF, this outcome remains under-reported in current HFrEF therapeutic RCTs. This observation calls for an effort to develop and to mandate tailored pragmatic definitions of granular stroke outcomes to be included in the protocols of HFrEF trials.

TRANSLATIONAL OUTLOOK 2: As no effective therapeutic strategy is currently available to prevent stroke among HFrEF patients, dedicated research to find effective treatments is dearly needed to address this ominous comorbidity.

TRANSLATIONAL OUTLOOK 3: Several characteristics of HFrEF severity predict stroke incidence, highlighting the potential to identify a subset of HFrEF patients at higher stroke risk that might benefit from prophylactic anticoagulation. Further research is needed to explore this hypothesis.

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KEY WORDS **beta-blockers, heart failure with reduced ejection fraction, mineralocorticoid-receptor antagonists, randomized controlled trial, renin-angiotensin-aldosterone inhibitors, stroke**

APPENDIX **For expanded Methods and Results sections as well as supplemental figures, tables, and references, please see the online version of this paper.**